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**Hernia through the Incisura of the Tentorium Cerebelli in Connection with Craniocerebral Trauma** . . . . . 699
*Donald Munro and Warren Sisson, Jr.*

**Canicola Fever: Report of First Case in Connecticut and Review of the Literature** . . 708
*Martin E. Gordon*

**Tuberculous Meningitis: Treatment of Spinal Block with Intrathecal Administration of Tuberculin** . . . . . 715
*Earnest C. Atkins and Martin M. Cummings*

**Medical Progress: Tuberculosis** . . . . . 718
*Donald S. King*

**By the London Post** . . . . . 740
**Boston Medical Library** . . . . . 742
**Notices** . . . . . 743

**Medical Intelligence:**

**Hiccups Complicating Myocardial Infarction.** . . . . . 726
*Harold R. Swan and Leo H. Simoson*

**Doctors Afield: Oliver Goldsmith** . . . . 728
*Joseph Garland*

**Case Records of the Massachusetts General Hospital** . . . . . 730

**Editorials:**

*Choice of Therapy for Pneumonia* . . . . . 736
*Pastor and Physician* . . . . . 738
*Nursing Fellowship Fund.* . . . . . 739
Ex Libris: *James F. Ballard* . . . . . 740

**Massachusetts Department of Public Health** . 742
**Correspondence** . . . . . 743

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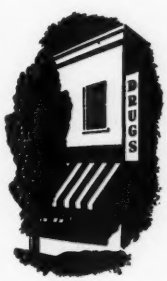


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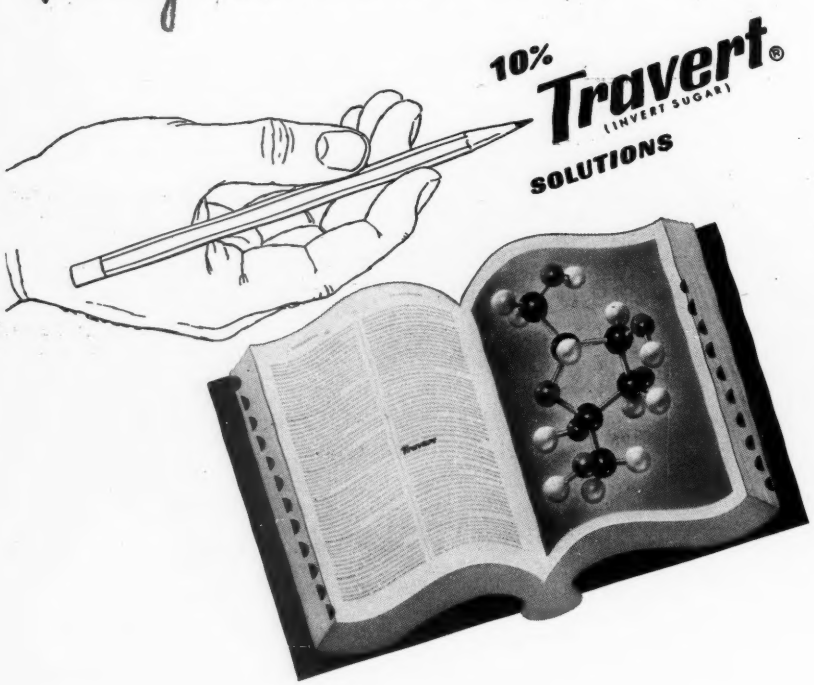


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# HERNIA THROUGH THE INCISURA OF THE TENTORIUM CEREBELLI IN CONNECTION WITH CRANIOCEREBRAL TRAUMA

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BOSTON

THE late Clovis Vincent and his co-workers in 1930[1] and again in 1936[2] called attention to the dangers inherent in the herniation of a part of one temporal lobe through the incisura of the tentorium cerebelli. Since then LeBeau,[3] LeBeau and Houdart,[4] Guiot and Janny,[5] Jefferson,[6] Zwan,[7] Schwarz and Rosner,[8] Evans and Scheinker,[9] Scheinker,[10] Freedman[11] and Reid and Cone[12] have written on this matter. Zwan,[7] Evans and Scheinker,[10] Freedman[11] and Reid and Cone[12] however, are the chief authors that we have come across who have considered such herniation in its relation to trauma. Zwan reports its occurrence in connection with a series of 43 subdural hematomas, 33 of which had been present two months or longer, 16 with and 17 without a history of antecedent trauma. The latter, therefore, are much more analogous to tumors than they are to the episodes of acute craniocerebral injuries, and as such their significance as examples of trauma is diminished. Evans and Scheinker discuss a series of acute cases — 6 in number — of extradural and subdural hematomas. They, like Zwan, draw from their experience certain conclusions relative to the diagnosis, treatment, prognosis and pathology of incisural herniation in general but are obviously handicapped by a lack of material. Freedman reports 16 examples of acute craniocerebral injuries, 15 of which were associated with meningeal hemorrhage and 1 with a dissolution of one temporal lobe. He is the only one to describe recurrent attacks of decerebration. Finally, Reid and Cone, whose interest is in the cause of unilateral dilatation of the pupil, refer to 9 of their cases, all of which showed such dilatation ipsilateral to an expanding cerebral lesion at some distance from the midbrain. Three case histories are given in some detail. Two of the patients each had an extradural cerebral hematoma, and the third a frontal abscess. All had temporal incisural hernias. The authors also include an excellent bibliography.

TABLE 1. *Material.*

| BASIS OF DIAGNOSIS | TRAUMATIC CASES | TUMOR | SPONTANEOUS HEMORRHAGE | OCCLUDED CAROTID ARTERY | NOT CLASSIFIED | TOTALS |
|---|---|---|---|---|---|---|
| Clinical verification | 76 | 15 | 0 | 0 | — | 91 |
| Operative verification | 21 | 1 | 0 | 0 | — | 22 |
| Autopsy verification | 54 | 56 | 19 | 7 | — | 136 |
| Total verifications | 151 | 72 | 19 | 7 | — | 249 |
| No hernia | 8 | 1 | 0 | 2 | 9 | 20 |
| Grand totals | 159 | 73 | 19 | 9 | 9 | 269 |

## MATERIAL

Our material consists of 314 cases. Sixty-seven are used as source material for data on operative results, 44 being used solely for this purpose and the remainder employed for both this purpose and an analysis of symptoms. The 67 were divided according to pathogenesis as follows: trauma, 51; tumor, 10; spontaneous cerebral hemorrhage, 4; and occluded carotid artery, 2.

Two hundred and sixty-nine cases have been analyzed in detail (Table 1). In 158 the presence of a herniation of the temporal cortex through the tentorial incisura has been confirmed either by operation (22 cases) or by autopsy (136 cases), and 20 other patients have been proved not to have had a similar herniation — in 8 by operation and in 12 by autopsy. An unconfirmed clinical diagnosis of

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incisural herniation was made in the 91 remaining patients.

One hundred and fifty-nine of the 269 patients were under treatment for a craniocerebral injury, 73 for cerebral and cerebellar tumors, 19 for spontaneous cerebral hemorrhage, and 9 for occlusion of one internal carotid artery. Nine were not classified.

### Etiology of Incisural Temporal Herniation

An understanding of the method of formation of an incisural herniation is essential to the early recognition of its need for treatment. It has been suggested by Dr. Raymond D. Adams,[13] and we are in full agreement with him, not only that it is the increase in the solid contents of any one meningeal compartment that leads to a herniation of the cerebral or cerebellar cortex through any of the meningeal or osseous bottlenecks associated with the skull and its intracranial cavities, but that this condition is preceded by a lateral, downward or upward movement of the involved cortex that may stop short of an actual herniation.

In patients with incisural temporal herniations this premonitory adjustment is evidently a reversible condition in which a clinical diagnosis can be no better than presumptive. We have been unable to verify this concept, however, except on *post hoc propter hoc* grounds, but as a working hypothesis it has already proved its worth. In its support we can cite the occurrence of an ipsilateral hemiplegia, which disappears with no more than the surgical removal of the clot in certain cases of cerebral extradural and subdural hematomas and in particular, those patients of the former group in whom an earlier contralateral hemiplegia has changed into an ipsilateral paralysis as the disease progressed.

In addition, it appears that the clinical and experimental observations of Reid and Cone,[12] as well as certain unpublished experimental work done on cats by Ford and Bailey,[14] bear this out so far as the temporal incisural herniation is concerned. With the aid of the Forbes window the former authors implanted an expansible but collapsed balloon over the surface of a monkey's cerebrum. With this arrangement, they could alter the intracranial pressure at will. It was apparent that such an addition to the supratentorial contents of the meningeal cavity caused a shift of the cerebrum to the side opposite that of the balloon and, at the same time, forced the supratentorial cortex downward, jamming the ipsilateral temporal cortex into the bottleneck formed by the incisural opening and, as it were, rolling the inferolateral part of it under, medially and downward in relation to the incisural edge. They and Ford and Bailey[14] observed that this produced third-nerve compression. The latter, moreover, hold that ischemia, focal and spreading necrosis, thrombosis and hemorrhages develop in the brain stem in that order and not, as is usually thought, in the reverse order of edema, thrombosis, hemorrhage and ischemic necrosis. Ford[15] believes that this movement represents the effect of converging and opposing forces with the resulting shift of the brain taking place in the direction of their resolution. In line with this concept he visualizes herniation of the temporal and adjoining cortices through the incisura as taking place when the increased content is lateral to and its exertion of pressure diagonal to the mid-sagittal plane. By the same token he believes that, if the increased content is so placed as to be directly in the midline and to exert its pressure along the sagittal plane, the bottleneck is found at the foramen magnum, and the herniation is of the cerebellar tonsils. We agree with this theory in so far as the incisural herniations are concerned although we do not believe that it gives enough weight to the importance of the resistance offered by the incompressible subtentorial column of cerebrospinal fluid. So far as the cerebellar herniations are concerned, and although it is undoubtedly possible that they are caused as predicated by Ford, — indeed we have had 3 cases in this series that appear to support his explanation, — and whether they are downward through the foramen or upward through the incisura, we believe that they are best understood by ascribing the chief motivating force to the increased bulk of tissue that is practically always present in the posterior fossa. The movement is further influenced by the delicate balance that is maintained between the opposing downward pressure of the supratentorial column of cerebrospinal fluid and the upward counterpressure of the incompressible column of cisternal and spinal cerebrospinal fluid. A further complication is produced by the reduction in the avenues of communication between the source of the fluid in the lateral ventricles on the one hand and its distribution and absorption throughout the subarachnoid spaces on the other.

Our contention, therefore, is that an early increase in bulk of — for example — the contents of the right temporal fossa moves the brain and the upper brain stem laterally to the left. This forces the left side of the brain stem against the left edge of the incisura, compresses the left pyramidal tract and may produce a right-sided or ipsilateral paralysis. Further swelling in the right temporal cortex now squeezes the inferomedial cortex downward, — expansion in all other directions being impossible, — and actual herniation through the incisura starts. Interference with the cerebrospinal-fluid circulation follows. The right lateral ventricle is compressed and reduced in size, and the venous circulation is interfered with locally. Edema, thrombosis and hemorrhage then develop in the herniated cortex and brain stem, possibly to be succeeded in turn by interference with the arterial circulation and ischemic necrosis of the brain stem and occipital

lobe. Decerebration follows. Resistance to this herniation of the temporal cortex is offered by the cerebrospinal fluid, which is trapped beneath the tentorium and which is supported in its turn by the column of cerebrospinal fluid that extends down the spinal subarachnoid space and that lies in the basilar cisterns. Thus, we have found, as first described by LeBeau, that in such patients, when operated upon prior to the onset of decerebration (as well as after), either a stab wound of the tentorium or a reduction of the herniated cortex while in its earliest stages has released a significant quantity of trapped cerebrospinal fluid under pressure, either through the stab wound or through the newly opened incisura, with resultant reduction to low levels of a previously high supratentorial intracranial pressure and an immediate and marked improvement in the patient's general condition. Although lumbar drainage of cerebrospinal fluid will be dangerous but not necessarily lethal during the early stages before the incisural cerebrospinal-fluid block has become virtually complete, it is fatal during the latest stages. The difference in its effect is dependent upon whether or not the lumbar drainage destroys the resistance to further herniation by removing the support offered by the infratentorial column of cerebrospinal fluid. To produce either a dangerous or lethal effect, however, at least the start of a herniation must be present at the time the lumbar drainage is instituted. If it is not present, the lumbar drainage will be beneficial in that it causes a general reduction of intracranial pressure with its salutary effect on the oxygenation of the brain, the re-establishment of the previously impaired cerebrospinal-fluid-absorption mechanism, the reduction of venous congestion and a correction of the altered osmotic relations between the capillary contents and the perivascular and intracellular fluids. Once the hernia is established beyond this point, however, the only hope of correction without a fatal outcome lies in the mechanical widening of the bottleneck, with reduction of the herniation by incision of the incisural ring. A recent experience not included in this series of cases emphasizes this fact. A patient who was suffering from traumatic cerebral subdural and intracortical hemorrhages was found at operation for the former to have a temporal incisural hernia as evidenced by the demonstration of some 40 cc. of bloody cerebrospinal fluid trapped under pressure beneath the tentorium. In consequence, the incisural edge was incised, but for some reason the incision was an extremely short one, extending laterally from the incisura no more than 0.5 cm. The patient improved markedly for three days, and her condition then began to get worse again, the chief symptoms being an increase in coma and respiratory difficulty. A cerebrospinal-fluid pressure of less than normal was repeatedly demonstrated on lumbar puncture. Five days after the first operation a re-exploration was performed. Again, bloody cerebrospinal fluid in the amount of 30 to 40 cc. was found trapped under pressure beneath the tentorium, and a recurrent incisural herniation was demonstrated. The old incisural-tentorial incision was extended laterally to the medial edge of the lateral sinus, and the hernia reduced. The patient died twelve hours later, having suffered from total respiratory paralysis for the last six hours. At autopsy there was no herniation of the temporal cortex through the incisura and no brain-stem compression, but there was a foraminal herniation of the cerebellar tonsils. Thus, it appears that with the failure to enlarge the incisural bottleneck sufficiently at the first operation, the incisural herniation had recurred and was followed shortly by the foraminal hernia.

Since the preliminary lateral movement of the supratentorial cerebral tissue and the similar downward or upward movement of the cerebellar cortex cannot take place without an original increase in the solid contents of the respective meningeal compartments, an actual herniation, whether laterally beneath the falx, downward through the incisura or foramen magnum or upward through the incisura, cannot develop in its turn without the driving force inherent in a still further increase in bulk of the contents of the involved meningeal compartment. Thus, cerebellar tumors, as they increase in size, characteristically produce herniation of the tonsils downward through the foramen magnum or of the upper surface of one or both hemispheres upward through the incisura of the tentorium. Continuing increase in the contents of one frontal fossa whether by tumor, clot or local swelling from contusion or laceration of the brain produces a herniation laterally of the medial surface of a frontal lobe beneath the falx. Similar increase in bulk of the contents of a temporal fossa causes squeezing of the inferomedial surface downward through the incisura of the tentorium. Generalized excessive supratentorial increase in bulk will produce the two latter herniations simultaneously, and if it is equalized between the two sides may produce a foraminal hernia. All these conditions are late ones, and when once established are irreversible, in the absence of operative relief, so far as return of function goes, although they are not necessarily fatal.

These latter data are recapitulated here only to point out that the picture as commonly recognized is a late one — perhaps not so late as to preclude continued life if proper therapy is provided in time, but usually too late to permit the resumption of normal cerebral activity. Since such decerebration is virtually death in all but name, some other and earlier stage of the development of a herniation has to be recognizable before treatment can be expected to be effective.

## Incidence in Patients with Craniocerebral Injuries

The frequency with which incisural temporal herniation occurs as a complication of craniocere-

bral injuries cannot be accurately estimated at present. Clinical evidence for or against its recognition is completely unreliable. The only certain way to determine its presence is by operation or by autopsy. In the living patient this requires either a stab wound of one leaf of the tentorium, with the demonstration of the escape of a significant amount of cerebrospinal fluid that has been trapped under pressure in the posterior fossa, or the same findings on operative withdrawal of the herniated cortex from within the incisura. After death, post-mortem verification necessitates autopsies on virtually 100 per cent of all patients with cerebral disease or injury. Moreover, the pathologist must remove the brain in such a way as to leave the hernia intact, because it is not enough to depend only on the appearance of the allegedly herniated cortex for a diagnosis. The presence of a Kernohan notch, for example, is not constant in all such lethal herniations, and its absence cannot be accepted as *prima facie* evidence of the absence of a herniation. It is also probable that patients in whom the earlier stages of herniation are present either may completely recover after spontaneous reduction of the hernia, particularly if such excess contents of one temporal fossa as an extradural or subdural clot has been removed at operation, or may improve temporarily only to die subsequently of the associated cerebral lesion. The figures presented herewith, therefore, cannot be regarded as conclusive but do appear to be indicative. They cover the years from January, 1947, to November, 1951 — four years and ten months. During this period 134 patients with cerebral subdural hematomas, 18 with cerebral extradural hematomas, and 224 with lacerated brains have been treated in the Neurosurgical Department of the Boston City Hospital. Of these 376 patients, 62, or approximately 17 per cent, were proved to have had a temporal incisural herniation. This figure undoubtedly errs on the side of conservatism since adequate autopsies were not done in 100 per cent of the fatal cases. Twenty-five per cent, or 34 of 134 patients with subdural hematomas, 44 per cent, or 8 of 18 patients with extradural hematomas, and 9 per cent, or 20 of 224 patients with a lacerated brain, are known to have had a temporal incisural herniation. Even with this small series it is apparent that the sudden addition of a mass of free or clotted blood to the normal contents of one temporal fossa predisposes to herniation of the temporal cortex through the incisura in a significant number of cases.

In addition, during the same period, there were known to be 3 patients without an incisural but with a foraminal herniation. One had a cerebral subdural hematoma complicated by a proved herniation of the cerebellar tonsils through the foramen magnum as well as of the medial surface of one frontal lobe beneath the falx. Each of the other 2 had a severely lacerated brain with a tonsillar herniation through the foramen magnum. These patients were the only ones with proved foraminal herniations in this group.

TABLE 2. *Signs and Symptoms.*

| CLASSIFICATION | TOTAL NO. OF CASES | NECK | | DILATED PUPIL | | | PARALYSIS | | | BABINSKI REFLEX | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | STIFF | SUPPLE | UNILATERAL | BILATERAL | NEITHER | HEMIPLEGIA | QUADRIPLEGIA | NEITHER | UNILATERAL | BILATERAL | NEITHER |
| | % | % | % | % | % | % | % | % | % | % | % | % |
| | | | | | | | | | | Symptoms in Patients with | | |
| Traumatic | 54 | 54 | 46 | 53 | 17 | 30 | 70 | 20 | 10 | 42 | 49 | 9 |
| Tumor | 56 | 20 | 80 | 28 | 4 | 68 | 64 | 9 | 27 | 34 | 33 | 33 |
| Spontaneous hemorrhage and occluded carotid artery | 19 26 7 | 27 | 73 | 40 | 8 | 52 | 76 | 8 | 16 | 35 | 46 | 19 |
| Totals | 136 | 33 | 67 | 40 | 10 | 50 | 67 | 13 | 20 | 37 | 42 | 21 |
| | | | | | | | | | | Symptoms in Patients with | | |
| Traumatic | 97 | 44 | 56 | 46 | 23 | 32 | 65 | 21 | 14 | 18 | 64 | 18 |
| Tumor | 15 | 29 | 71 | 34 | 7 | 57 | 33 | 0 | 66 | 20 | 20 | 60 |
| Totals | 112 | 42 | 58 | 42 | 22 | 35 | 61 | 19 | 20 | 19 | 55 | 26 |
| | | | | | | | | | | Symptoms in Patients without Hernia | | |
| No hernia | 20 | 33 | 67 | 17 | 6 | 77 | 70 | 5 | 25 | 28 | 33 | 39 |

## DIAGNOSIS

If our hypothesis is accepted and if treatment is to be effective, the diagnosis of an incisural hernia must be made before the herniation is complete, and certainly before permanent damage has been done to the brain stem — and should be made, if possible, even before the herniation has progressed beyond its earliest development. Our material, therefore, has been analyzed from the point of view of certain signs and symptoms in an attempt to set up a clinical entity that can be diagnosed early and with reasonable accuracy.

## SIGNS AND SYMPTOMS

### *In General*

Previous students of this problem have described a set of signs and symptoms (Table 2) that have been considered significant and diagnostic. These include a history of a deepening coma and the demonstration of a stiff neck, a unilaterally dilated

pupil, a hemiplegia, convulsive seizures and decerebration, together with a group of abnormalities associated with disordered function of the autonomic nervous system, including respiratory and circulatory irregularities, fever and vomiting. To these we have added the demonstration of a unilateral or bilateral Babinski reflex, of quadriplegia and of what we have termed a "critical lumbar puncture." All but the last require no further explanation.

A "critical lumbar puncture" developed as an entity in this study in connection with an attempt to determine the causal relation between a lumbar puncture (with which a reduction in intracranial pressure was associated) and the onset of a temporal incisural herniation. We have found that a lumbar puncture accompanied by intentional or unintentional cerebrospinal-fluid drainage is a "critical" puncture and, therefore, presumes a diagnosis of incisural temporal herniation when any one or more of the following criteria are present: first, a definite, unmistakable increase in coma immediately after the puncture; secondly, a measured minimal intracranial pressure of 300 mm. of cerebrospinal fluid; thirdly, intentional or unintentional reduction of the intracranial pressure to 0 mm. of cerebrospinal fluid by the withdrawal of any amount — no matter how small or large — of cerebrospinal fluid; fourthly, the sudden unexplained permanent cessation of the flow of cerebrospinal fluid from the needle during a lumbar puncture; fifthly, the sudden unexplained permanent reduction of a high cerebrospinal-fluid pressure to 0 during a lumbar puncture; and, finally, the onset of respiratory irregularities, a fixed dilatation of one pupil or the development of a hemiplegia (particularly if it is ipsilateral to a known cerebral clot) or a quadriplegia with or without decerebrate fits during or immediately after a puncture.

For purposes of comparison between the various categories of cases the incidence of the various signs and symptoms is presented as the number per 100 occurring in all cases as well as in the various separate groups. The total number of cases in which any one sign or symptom appeared has been limited to those about which a definite positive or negative statement has been available. Patients in whose records no comment has been made about any given sign or symptom have been excluded from consideration in relation to that particular item.

### *In All Proved Temporal Incisural Hernias*

There were 158 cases with a proved temporal incisural hernia. In 22 of these the herniation was demonstrated at operation, but, because of the theoretical possibility of errors in observation, these cases are not included in this immediate analysis. The accompanying data, therefore, are based on 136 cases in which the herniation was demonstrated at autopsy (Table 2). It is apparent from these figures that in the presence of a temporal incisural hernia, the *neck* was more apt to be supple than stiff; that *unilateral or bilateral fixed dilatation of the pupils* was not constant and was only as common as nondilatation; that *hemiplegia* was five times as common as quadriplegia and three times as common as no paralysis; that a *bilateral Babinski* sign was twice and, when taken in conjunction with a unilateral sign, three times as common as its absence; that *seizures* occurred in less than half the cases; and that *decerebration* occurred in approximately a third. Functional abnormalities of the autonomic system were manifested by *respiratory irregularities* in about three fourths, *fever* in a sixth, *vomiting* in about a quarter and *circulatory variations* in about a fourth of the patients. *Increasing coma* was virtually constant and a *critical lumbar puncture* was present in slightly less than half the cases.

TABLE 2. (*Concluded.*)

| CLASSIFICATION | SEIZURES | | DECEREBRATION | | AUTONOMIC-SYSTEM ABNORMALITIES | | | | | | CRITICAL LUMBAR PUNCTURE | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | YES | NO | YES | NO | NONE | RESPIRATORY | CIRCULATORY | FEVER | VOMITING | INCREASING COMA | YES | NO |
| | % | % | % | % | % | % | % | % | % | % | % | % |
| Hernia Verified by Autopsy | | | | | | | | | | | | |
| Traumatic | 38 | 62 | 39 | 61 | 2 | 84 | 20 | 10 | 16 | 98 | 62 | 38 |
| Tumor | 52 | 48 | 16 | 84 | 13 | 64 | 28 | 21 | 32 | 98 | 32 | 68 |
| Spontaneous hemorrhage and occluded carotid artery | 20 | 80 | 12 | 88 | 8 | 58 | 19 | 19 | 38 | 96 | 37 | 63 |
| Totals | 41 | 59 | 24 | 76 | 8 | 70 | 23 | 16 | 27 | 98 | 44 | 56 |
| Hernia as Verified Clinically | | | | | | | | | | | | |
| Traumatic | 43 | 57 | 41 | 59 | 2 | 86 | 23 | 33 | 28 | 100 | 57 | 43 |
| Tumor | 20 | 80 | 8 | 92 | 0 | 93 | 40 | 33 | 73 | 99 | 38 | 62 |
| Totals | 38 | 62 | 36 | 64 | 2 | 87 | 25 | 33 | 35 | 99 | 55 | 45 |
| as Verified by Autopsy and Operation | | | | | | | | | | | | |
| No hernia | 37 | 63 | 12 | 88 | 17 | 78 | 17 | 22 | 16 | 100 | 35 | 65 |

### *In All Patients Proved Not to Have Had a Temporal Incisural Hernia*

A similar analysis was made in 20 patients in whom a clinical diagnosis of incisural herniation

had been made but who proved at autopsy or operation (in the survivors) to have had no herniation (Table 2). The difference between this and the preceding group was not significant. As in the patients with proved herniation, the *neck* was more often supple than stiff, *hemiplegia* was three times as common as no paralysis, the *Babinski reflex* was more often present than not, *seizures and decerebration* were present in the minority, and the commonest autonomic irregularity was *respiratory* in type. *Deepening coma* was present in all cases.

The only significant differences between the two groups were found in the *condition of the pupil*, which was not dilated in three quarters of the nonherniated patients, and the signs of *autonomic-nervous-system malfunctioning*, which were entirely absent in 17 per cent of the nonherniated as opposed to 8 per cent of the herniated patients. *The critical lumbar puncture* was present in only about a third of such patients.

### *In Cases with Clinical but Not Proved Temporal Incisural Hernias*

Analysis of the 112 cases in which the diagnosis was made on clinical evidence only, but in which proof of the presence of a hernia was otherwise lacking, is not significantly different statistically from that of the proved cases (Table 2). This includes 29 patients in whom the herniation was demonstrated at operation but not at autopsy.

### *Summary*

In summary and on the basis of this analysis and of this series of 268 patients the only signs or symptoms that can be considered characteristically diagnostic of an incisural temporal herniation regardless of the underlying disease are a *unilateral or bilateral fixed dilatation of the pupils*; *decerebration*; the presence of a *critical lumbar puncture* and the virtually constant presence of some one of the so-called *autonomic symptoms*. This is hardly enough to justify either a diagnosis or an exclusion of this lethal complication on purely clinical grounds.

### *Incisural Herniation in Association with Tumors*

Signs and symptoms in this group agree in the main with the general occurrence rate for all proved herniations (Table 2). The exceptions are the 2:1 absence of a *dilated pupil*, the presence of 13 per cent of patients with no *autonomic symptoms* or signs and the 2:1 absence of a *critical lumbar puncture*.

### *Incisural Herniation in the Presence of Either Spontaneous Cerebral Hemorrhage or Occlusion of One Internal Carotid Artery*

The signs and symptoms in this group (Table 2) agree closely with those of the traumatic group presented below. This agreement, on the one hand, and the disagreement with the tumor group outlined above, on the other, is to be expected because of the similar sudden onset and associated circulatory involvement that is common to both cerebral injury and to interruption of the cerebral circulation. The symptomatic exceptions are that the *neck* is supple in three fourths and a *critical lumbar puncture* is present in a third of the patients in this nontraumatic group. It is also less common to find a *dilated pupil* in this group, the occurrence rate resting between the high rate of trauma and the low one of tumors.

### *Incisural Herniation in Association with Trauma*

The diagnosis on the basis of clinical evidence (Table 2) appears to be a little easier to make when a herniation develops in association with a craniocerebral injury. Thus, the *neck* is more often stiff than not; unilateral *pupillary dilatation* is present in over half the cases; *hemiplegia* or *quadriplegia* as well as a *unilateral* or *bilateral Babinski* response is virtually certain to be present; and *respiratory abnormality* occurs in about nine tenths and a *critical lumbar puncture* in two thirds of these patients. The probable diagnosis of incisural herniation should be made in craniocerebral injuries, therefore, in the presence of increasing coma, the development of a hemiplegia or quadriplegia, the demonstration of a stiff neck, a unilateral and particularly a bilateral Babinski reflex and any respiratory irregularity or abnormality. If to these signs is added a "critical lumbar puncture" the diagnosis is virtually mandatory, and operative therapy is therefore also mandatory.

TABLE 3. *Results of Operation.*

| YEAR | TOTAL CASES | MORTALITY | POSITIVE TENTORIAL STAB WOUND | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | PATIENT DECEREBRATE AT OPERATION | | | INCISURA CUT | | | MORTALITY | | PATIENT SURVIVED | | |
| | | % | *Yes* | *No* | *Total* | *Yes* | *No* | *Total* | *Number* | % | *Normal* | *Normal with Residual* | *Institutionalized* |
| 1949 ..... | 6 | 66 | 2 | 2 | 4 | 4 | 0 | 4 | 3 | 75 | 0 | 1 | 0 |
| 1950 ..... | 9 | 33 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 1951 and 1952 . | 50 | 56 | 7 | 7 | 14 | 19 | 1 | 20 | 11 | 55 | 4 | 2 | 3 |
| Totals ..... | 65 | 54 | 9 | 9 | 18 | 23 | 1 | 24 | 14 | 58 | 4 | 3 | 3 |

2 other patients (1 in 1950 and 1 in 1951), though clinically diagnosed as tentorial herniations, proved to have only tonsillar herniations.

Additional support for the diagnosis may be gleaned from the type of supratentorial disease that is present. As noted above, of 62 proved incisural hernias that occurred in connection with craniocerebral injuries, 34 were associated with cerebral subdural hematomas, 8 with cerebral extradural hematomas, and 20 with lacerated brains. Of 76 clinically diagnosed incisural herniations that occurred in connection with craniocerebral injuries, 28 were associated with cerebral subdural and 3 with cerebral extradural hematomas, 7 with gunshot wounds of the brain and 30 with a lacerated brain. The presence of a cerebral subdural hematoma or a lacerated brain lends weight, therefore, to the presumptive diagnosis of a temporal incisural herniation.

TABLE 3. (*Concluded.*)

| YEAR | NEGATIVE TENTORIAL STAB WOUND | | | | | | | | | | TOTAL | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | PATIENT DECEREBRATE AT OPERATION | | | INCISURA CUT | | | MORTALITY | | PATIENT SURVIVED | | | DIED | SURVIVED | | |
| | *Yes* | *No* | *Total* | *Yes* | *No* | *Total* | *Number* | *%* | *Normal* | *Normal with Residual* | *Institutionalized* | | *Normal* | *Normal with Residual* | *Institutionalized* |
| 1949 ..... | 1 | 1 | 2 | 2 | 0 | 2 | 1 | 50 | 0 | 0 | 1 | 4 | 0 | 1 | 1 |
| 1950 ..... | 3 | 6 | 9 | 4 | 5 | 9 | 3 | 33 | 3 | 1 | 2 | 3 | 3 | 1 | 2 |
| 1951 and 1952 | 14 | 16 | 30 | 25 | 5 | 30 | 17 | 57 | 10 | 1 | 2 | 28 | 14 | 3 | 5 |
| Totals ... | 18 | 23 | 41 | 31 | 10 | 41 | 21 | 51 | 13 | 2 | 5 | 35 | 17 | 5 | 8 |

## TREATMENT

In the past, effective therapy of this condition has been delayed, first, because the presence of an incisural herniation in connection with a craniocerebral injury has not been suspected and hence the diagnosis has not been considered and, secondly, because a practical method of reducing the hernia was not available. The presence of a significant number of such hernias as a cause of death was first forcibly called to our attention by the pathologist in 1947. In this year a verified incisural herniation was reported to us as a cause of death in 10 of our patients with craniocerebral injuries. In 1948, 10 similar cases were reported. In these same years a review of the appropriate records made in the light of the diagnostic criteria given by LeBeau for tumors yielded 19 other patients who, by clinical criteria, appeared to have died as the result of incisural herniation but in whom post-mortem verification was lacking. It was apparent that some method would have to be devised to deal with this serious problem.

Pending the collection of a sufficient number of cases from which diagnostic criteria could be adduced a review of the available methods of treatment was undertaken. It appeared that the choice lay between excision of the offending temporal lobe as advised by Jefferson and section of the incisural ring by an approach from the temporal fossa over the petrous ridge as advised by LeBeau and his group. Neither one of these appeared to us to be practical in the patient with a craniocerebral injury. Indeed, we had tried the latter method once or twice but had been unable even to visualize the incisura. It was decided, therefore, to investigate the possibility of an approach by way of the occipital fossa, remaining constantly posterior to the petrous ridge, and at the same time to take advantage of the recommendations by Le Beau that the trapped subtentorial cerebrospinal fluid be released by a stab wound through the leaf of the tentorium prior to any attempt at retraction of the occipital lobe and visualization of the incisural ring.[16] This was first carried out in 1949 (Table 3). At that time, because of our unfamiliarity with the problem and lack of confidence in the method, the operation was limited to patients who were *in extremis* and already decerebrate, in the hope of thus learning whether the method was at least life saving. Seven patients were operated upon by this method during that year. All but 1—a patient with a tumor—had craniocerebral injuries. One was discharged alive and well. Three died within a week of the operation. Two others lived for ten months but never regained consciousness, 1 dying in the hospital and the other being discharged to another public institution. The patient with the tumor turned out not to have a hernia and has not been counted. During the same period, 12 other patients were proved at autopsy to have had undiagnosed and untreated hernias. It was apparent that the method was practical and possibly life saving. It was continued in use, therefore, but now an attempt was made to make the clinical diagnosis earlier, more accurately and more frequently.

In 1950, 10 patients were operated upon with a clinical diagnosis of incisural herniation (Table 3). The diagnosis was not verified in 9 by either operation or autopsy, but the tenth proved at autopsy to have had a tonsillar herniation through the foramen magnum. All but 2, 1 of whom had a spontaneous cerebral hemorrhage and the other an occluded carotid artery, had craniocerebral injuries. Six were discharged alive from the hospital, 2 of

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them having to be institutionalized because of permanent cerebral damage. Three died within a week of the operation. Two other patients seen during this period were proved at autopsy to have had undiagnosed and untreated incisural hernias. Although this experience did not indicate any significant increase in diagnostic acumen it did show that the operation could be performed with relative safety in the absence of an incisural herniation. It could also be argued, since the number of such hernias found at autopsy was materially less than that in the previous year and since the majority of the patients that had been operated upon had survived, that possibly the treatment had been successful because it had been actually rendered during the preherniation stage. The tentative conclusion was reached, therefore, that the operation should be undertaken primarily as a prophylactic measure and the attempt should be made to deal with an incisural herniation before it actually developed and while it was in the premonitory preherniation stage.

Accordingly, in 1951 and the first quarter of 1952, all patients operated upon as a means of treatment of a craniocerebral injury or a cerebral tumor had a stab wound made in one tentorial leaf and, if it was at all possible to do so, the edge of the incisura divided, whether or not there was evidence of actual herniation (Table 3). On this basis, 50 such operations were performed. Twenty-two patients survived the operation for two months or more. Three others died decerebrate in the hospital three to six months after operation. Fourteen were normal and were discharged to their homes. Five had to be sent to other institutions for custodial care. Thirty patients had negative and 20 positive tentorial stab wounds. Forty-three were decerebrate at the time of operation, including the 28 who died in the hospital.

As our experience has increased we have accumulated certain data, the use of which can be expected to reduce both the morbidity and mortality of this condition in the future. Perhaps the most important contribution has been appreciation that the prolonged and powerful retraction of the occipital lobe necessary to see and cut the edge of the incisura in the presence of an edematous, swollen, protruding brain leads to extensive hemorrhage, softening and focal necrosis of the retracted tissue. In certain cases we feel sure that this necrosis has caused a fatal outcome that would not otherwise have occurred. With the instruments at hand we have not dared to cut the incisural edge blindly for fear of injuring the brain stem or of cutting the structures on and adjacent to it. The need for strong prolonged retraction of the occipitotemporal cortex, therefore, is a definite contraindication to sectioning the incisura. We have not had enough cases with divided communicating veins (the veins of L'Abbé and adjoining groups) to determine the effect of their closure with or without division of any or all of them. It is said, however, that such procedures lead to hemiplegia and hemianopia. Although it is certain that incisural section is more effective if done before decerebration sets in, it has been our experience that it should not be denied the patient who needs it even in the presence of decerebration. As noted above, not all our patients who were decerebrate at the time of incisural section remained so after the reduction of the hernia. An unexpected dividend has accrued to us in the tumor cases. This is the greater freedom with which we are able to perform and the increased therapeutic effect inherent in postoperative lumbar-puncture decompression. We feel sure that the convalescence of such patients, especially those who have had temporal-lobe tumors excised, has been materially simplified and shortened. Of the 51 patients (1 without an incisural but with a foraminal hernia) operated upon in 1952, 8 had tumors, 2 had a spontaneous cerebral hemorrhage, 1 had an occluded carotid artery and 39 had a craniocerebral injury.

TABLE 4. *Mortality.*

| TYPE OF CASE | TOTAL CASES | DEATHS FOLLOWING OPERATION | | | | | RECOVERIES | RECOVERIES WITH RESIDUAL | RECOVERY RATE |
|---|---|---|---|---|---|---|---|---|---|
| | | 24 HR. OR LESS | 24 HR. TO 1 WK. | 1 WK. TO 1 MO. | OVER 1 MO. | OPERATIVE MORTALITY | | | |
| | | | | | | % | | | % |
| Verified — no hernia | 15 | 3 | 3 | 1 | 0 | 40 | 7 | 1 | 53 |
| Probably no hernia | 28 | 8 | 7 | 0 | 2 | 54 | 9 | 2 | 40 |
| Total patients without hernias | 43 | 11 | 10 | 1 | 2 | 48 | 16 | 3 | 44 |
| Hernia present | 24 | 8 | 3 | 3 | 4 | 58 | 5 | 1 | 25 |
| Total operations | 67 | 19 | 13 | 4 | 6 | 54 | 21 | 4 | 37 |

## RESULTS

In estimating the effect of operative therapy on incisural herniation there are certain factors that must be evaluated in relation to the results. The first of these is the actual cause of death. With a heavy preponderance of patients with craniocerebral injury, often not referred for neurosurgical treatment until they are *in extremis*, the injury itself carries, even in the absence of such an opera-

tion as incisural section, an extremely high mortality. This is evidenced by the fact that 24 or 62 per cent of all deaths, in addition to 17 or 81 per cent of all operative deaths, occurred within forty-eight hours of the operation (Table 4). The importance of this aspect is emphasized by the realization that the commonest cause of the herniation was a meningeal clot. Such clots are notoriously difficult to recognize and in such acute injuries have an inherent mortality ranging from 40 to 55 per cent.[17, 18] In correcting for this cause all deaths occurring within two weeks of the surgery have been meticulously analyzed, and the death ascribed to the operation if appropriate and to other causes if not. This adjustment has fixed the number of deaths properly traceable to the operation at 23 (Table 5). The diagnoses of those that were eliminated were as follows: accidental hemorrhage from a cortical artery (1 case), Laënnec's cirrhosis (1 case), tonsillar herniation (2 cases), pulped brain (2 cases), inhaled vomitus, pneumonia, carcinomatosis, spontaneous coronary thrombosis, cerebrovascular accident, temporal-lobe abscess and effects of a pituitary adenoma (1 case each).

Our experience has further demonstrated that to obtain the greatest benefit from this therapy, the incisural section should be performed, if possible, prior to the onset of decerebration. This has been touched on above. It is emphasized by the figures derived from this larger number of patients operated on (Table 5). The corrected mortality among patients that were already decerebrate at the time of operation, whether a hernia was present or not, was 50 per cent. The corresponding rate in the nondecerebrate group was only 38 per cent. Further support for the performance of this procedure as a prophylactic measure is found in the fact that among the patients who were decerebrate but had no hernia, the operative mortality was 50 per cent, whereas in the similar group that was not decerebrate the operative mortality was only 30 per cent. It made no difference in these cases whether the incisura was cut or not — the figures were lower among the nondecerebrate patients. It is this group moreover that had been adversely affected by the occipital-lobe ischemic necrosis produced by excessive retraction. This has been mentioned above. The figures further suggest that a stab wound through the tentorial leaf and the demonstration of trapped cerebrospinal fluid under pressure — used, as in this series, to make or exclude the diagnosis of temporal incisural herniation — is a safe procedure if the patient is not already decerebrate and is an essential one whether decerebration is present or not.

TABLE 5. *Operations Corrected for Causes of Death.*

| CLASSIFICATION | FATAL CASES | | | SURVIVALS | | | TOTALS | | | MORTALITY | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | INCISURA CUT | INCISURA NOT CUT | TOTAL | INCISURA CUT | INCISURA NOT CUT | TOTAL | INCISURA CUT | INCISURA NOT CUT | TOTALS | INCISURA CUT | INCISURA NOT CUT | TOTAL |
| | | | | | | | | | | % | % | % |
| Decerebrate before operation: | | | | | | | | | | | | |
| No hernia | 6 | 1 | 7 | 6 | 1 | 7 | 12 | 2 | 14 | 50 | 50 | 50 |
| Hernia | 5 | 0 | 5 | 5 | 0 | 5 | 10 | 0 | 10 | 50 | — | 50 |
| Totals | 11 | 1 | 12 | 11 | 1 | 12 | 22 | 2 | 24 | 50 | 50 | 50 |
| Not decerebrate before operation: | | | | | | | | | | | | |
| No hernia | 5 | 1 | 6 | 7 | 7 | 14 | 12 | 8 | 20 | 42 | 13 | 30 |
| Hernia | 4 | 1 | 5 | 4 | 0 | 4 | 8 | 1 | 9 | 50 | 100 | 56 |
| Totals | 9 | 2 | 11 | 11 | 7 | 18 | 20 | 9 | 29 | 45 | 22 | 38 |
| All Cases: | | | | | | | | | | | | |
| No hernia | 11 | 2 | 13 | 13 | 8 | 21 | 24 | 10 | 34 | 46 | 20 | 38 |
| Hernia | 9 | 1 | 10 | 9 | 0 | 9 | 18 | 1 | 19 | 50 | 100 | 53 |
| Totals | 20 | 3 | 23 | 22 | 8 | 30 | 42 | 11 | 53 | 48 | 27 | 43 |

## CONCLUSIONS

We believe that temporal incisural herniation is a dangerous and important complication of craniocerebral injuries — particularly cases in which a meningeal clot or a lacerated brain forms a part of the pathological picture. We have presented evidence that the diagnosis must be presumed on the demonstration of certain signs and symptoms.

Once such a presumptive diagnosis has been made, operative division of one edge of the incisura is mandatory within six hours unless the patient takes a turn for the better, unless a stab wound of one tentorial leaf does *not* demonstrate cerebrospinal fluid trapped under pressure beneath the tentorium and unless it proves impossible to retract the occipital lobe without damage.

Such treatment is most effective if rendered as a prophylactic measure or, in any event, prior to the onset of decerebration. It should be afforded, except for the contraindication inherent in damage to the occipital lobe by forcible retraction, whenever a meningeal or intracortical clot is demonstrated in either temporal fossa or temporal cortex and when-

ever a tumor is removed from in or near a temporal fossa.


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## CANICOLA FEVER*

### Report of First Case in Connecticut and Review of the Literature


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HEPATOCELLULAR disease is often ascribed to a viral agent without adequate investigation. Leptospiral infections of the liver can simulate epidemic infectious or viral hepatitis and may occur more frequently than is usually suspected. It is the purpose of this communication to describe such an acute spirochetal infection and to point out its worldwide variations.

Canicola fever, or infection with *Leptospira canicola*, is similar to Weil's disease but is transmitted to human beings directly or indirectly by dogs. It may be differentiated from infection caused by *Lept. icterohaemorrhagiae* by serologic means. Over 200 cases have now been reported in the world medical literature.[1-21] A total of 26 cases have been mentioned to date in the American literature (Table 1).[4-7, 23, 24-32] The following is the first case reported from Connecticut.

### Case Report

M. K., a 28-year-old brass-factory worker, entered the hospital on July 26, 1949, with a chief complaint of "yellow skin and fever" of 2 weeks' duration. Three weeks prior to entry a shaking chill, followed by fever, drenching sweats and severe retro-orbital headache, suddenly developed. Injection of the eyes and marked pains in the calf were noticed. These were so excruciating that he could not bear his weight. Subsequently, anorexia, vomiting and a maximum daily temperature of 103°F. appeared. On the 5th day of the illness, dark-brown urine and obstipation appeared. On the 6th day jaundice was noted by his physician. On the 22d day he entered the hospital because of continued symptoms. He had sustained a traumatic puncture of the left eardrum 2 weeks prior to the onset of his illness and had been swimming in a stagnant bay‡ 5 days before the 1st symptom appeared. He had no known direct contact with dogs or other pets. The remainder of the history was noncontributory.

Physical examination revealed a thin, acutely ill man, who was deeply jaundiced. No perforation of the left tympanic membrane was seen. A Grade II systolic murmur was heard over the entire precordium. The liver edge was tender and palpable 4 fingerbreadths below the costal margin. A tender spleen was felt at the left costal margin. Moderate muscle wasting of the lower extremities was seen, but calf tenderness was absent. Neurologic and skin examinations were negative. A roentgenogram of the chest revealed no abnormalities of the heart or lungs.

The temperature was 102°F., the pulse 90, and the respirations 20. The blood pressure was 120/60.

Examination of the blood showed a white-cell count of 7900, with 77 per cent neutrophils, 19 per cent lymphocytes and 4 per cent monocytes; subsequent counts did not differ appreciably from this. The hemoglobin was 12 gm. per 100 cc. Urinalysis revealed a + test for albumin, with a few granular and hyaline casts, 3 to 5 red cells and occasional white cells per high-power field in the sediment. These elements disappeared by the 16th hospital day. The nonprotein nitrogen ranged between 25.5 and 31 mg. per 100 cc. A serologic test for syphilis was negative. The stools showed no occult blood, ova or parasites. Several blood cultures taken at the height of the fever were sterile. A complement-fixation test for amebiasis was doubtful. There was no disturbance of the bleeding and clotting times. Lumbar puncture on admission disclosed normal dynamics. The spinal fluid was light tan and clear. There was no pleocytosis or elevation of protein. Dark-field examination failed to reveal spirochetes. Young guinea pigs inoculated with spinal fluid and urine remained in excellent health during the 3-week period of observation. Serial serologic tests were performed by the Connecticut State Public Health Laboratories and confirmed by the United States Public Health Service Laboratories in Chamblee, Georgia. The remainder of the significant laboratory data are presented in Figure 1.

Therapy consisted of bed rest, 80 mg. of vitamin K parenterally each day and a diet high in proteins and calories. By the 5th hospital day there was a marked decrease in fever. Improvement in the myalgia, malaise and appetite followed. By the 10th hospital day the liver edge had receded to 2 fingerbreadths below the costal margin in the midclavicular line. A needle biopsy of the liver was performed uneventfully at this time, the 31st day of the illness. The section showed the lobular architecture to be well preserved (Fig. 2). There was mild hepatocellular damage. Numerous Kupffer cells were darkly pigmented with bile. Rare bile plugs were present in the bile canaliculi (Fig. 3). Inflammatory cells were entirely absent in the portal areas. The findings were


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mild, nonspecific hepatocellular damage, indicating a "healing hepatitis."

Clinical improvement was gradual, and the patient was discharged on the 75th day of illness.

Follow-up studies obtained on December 20, approximately 4 months after the onset of illness, and again in May, 1952, nearly 3 years after the infection, indicated that the patient still had residual easy fatigability and lassitude, as well as a general mental depression not present before his illness. Physical examination was within normal limits except for slight liver enlargement and tenderness.

Laboratory data, including electrocardiograms and x-ray films of the gastrointestinal tract, were normal. Liver-function tests were negative except for a ++ cephalin-flocculation test in 1952. Hamsters inoculated with the patient's 24-hour urine concentrates (in 1949 and 1952) remained alive and well. Repeated agglutination titers to *Lept. icterohaemorrhagiae* and *Lept. canicola* in 1950 and 1952 no longer showed significant titers (Fig. 1).

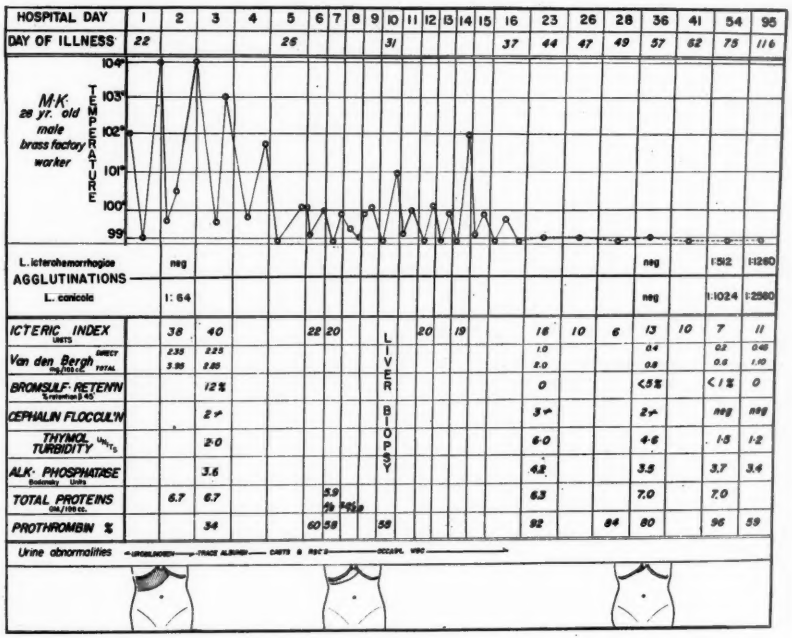


FIGURE 1. *Clinical Course in a Case of Canicola Fever. Liver-function improvement paralleled the clinical progress.*

## DISCUSSION

*Lept. icterohaemorrhagiae* and *canicola* have been studied with the electron microscope[33] and found to be identical in both morphology and motility.

It has been shown that leptospirae are capable of surviving and remaining virulent after three weeks in stagnant water as long as the pH remains near 7.0 and the temperature is not excessively cold. The organisms perish at a pH below 6.7.* [34]

*A sample of the stagnant water in which the patient in the case reported swam was found to have a pH of 7.1, compatible with survival of leptospiral organisms.

The dog transmits the disease to human beings through contact with contaminated urine; 15 to 40 per cent of dogs tested in various studies[4-7, 21, 26, 35-37] have been shown to have significant antibody titers to *Lept. canicola*. One intensive study[38] revealed that persons whose activities brought them in close contact with dogs demonstrated no significant titer. The relatively low incidence of the disease in human beings may be due to the fact that dogs shed leptospirae transiently and that their urines are too highly acid for survival of the organism.[34] The portal of entry is the broken skin or intact mucous membranes by contact with contaminated material. Transmission by the bite of a dog has been reported.[12] The case presented above is probably the eleventh case of canicola fever acquired while the patient was swimming.[17, 19-21, 28, 29] Transmission of *Lept. canicola* by the rat has been suggested by one group,[27] but the evidence presented seems tenuous.

The onset of canicola fever has been variously described as abrupt and stormy or insidious and mild. Usually, a sudden high fever, pronounced malaise, conjunctival or ciliary injection and severe muscular pain, characteristically involving the calves, are seen. Jaundice or hepatomegaly has

been present in many of the cases fully reported in the United States (Table 1). This is only rarely evident in cases reported from Europe, where meningeal irritation is the outstanding characteristic.[8, 16, 16-22] Beeson and Hankey[30, 31] have recently stressed the high incidence of so-called "benign aseptic meningitis" due to leptospirae. They were found in 6 of a total of 35 cases observed in an

TABLE 1. *Clinical Data in Cases of Canicola Fever Reported in the United States.**

| AUTHOR | LOCATION | YEAR | AGE OF PATIENT | SEX | OCCUPATION | MODE OF ONSET | CENTRAL-NERVOUS-SYSTEM SYMPTOMS |
|---|---|---|---|---|---|---|---|
| | | | *yr.* | | | | |
| Meyer et al.[5] | Stockton, California | 1938 | 28 | M | Veterinarian | "Influenza-like febrile illness" | — |
| Meyer et al.[6] | California | 1939 | — | M | Assistant veterinarian | "Undulant-fever-like disease" | — |
| Bruno et al.†[33] | New Orleans | 1943 | 63 | M | Night watchman | 2 wk. of mild malaise and cough; temperature of 102°F. | Mental cloudiness and convulsion |
| Tievsky and Schaefer[15] | Washington, D. C. | 1943 | 23‡ | M | Soda-factory worker | 1 wk. of cough, fever, chills and headache; temperature of 104°F. | Delirium and stupor but no nuchal rigidity; cerebrospinal fluid contained 14 to 60 cells per cubic millimeter. |
| Randall and Cooper[34] | ?Washington, D. C. | 1943 | No details given — owner of dog from which *Lept. canicola* (Strain A) isolated became seriously ill; leptospira demonstrated in patient's urine. | | | | |
| Rosenbaum[16] | San Antonio, Texas | 1946 | 44 | M | Army officer | Sudden fever (temperature of 103°F.), myalgia, anorexia, arthralgia and conjunctivitis of 5 days' duration | None (lumbar puncture not done) |
| Molner et al.[37] | Detroit | 1948? | No details given — of 78 proved infections, 2 were distinctly canicola fever (1 was fatal), and 2 other cases were equivocal. | | | | |
| Doerner and Hernandez[36] | New Orleans | 1947 | 47 | M | Fisherman, trapper and hunter | Cough, malaise, chills and fever (temperature of 106°F.), myalgia, headache and conjunctivitis | Patient restless and confused at times; lumbar puncture 5 mo. after illness showed cerebrospinal-fluid protein of 100 mg. per 100 cc. |
| Turrell and Hamburger[35] | Cincinnati, Ohio | 1947 | 32 | M | House insulator | Chills and fever, nausea and vomiting, myalgia and conjunctivitis | Delirium; 3 convulsions; lumbar puncture showed 400-810 white cells per cubic millimeter; cerebrospinal-fluid protein 50 mg. per 100 cc. |
| Rosenberg[19] | Washington, D. C. | 1946 | 17‡ | M | Trash collector | Fever (temperature of 103.5°F.), headache, pain and weakness in legs, conjunctivitis and bradycardia | Drowsiness, muscle spasm, weakness, positive Kernig sign; lumbar puncture showed 6-230 cells per cubic millimeter (86 per cent lymphocytes). |
| Rosenberg[19] | Washington, D. C. | 1948 | 33‡ | M | Window cleaner and veterinarian's helper | Sudden joint pains, fever (temperature of 102.4°F.), chills, myalgia, severe headache, anorexia with vomiting, conjunctivitis with bulbar hemorrhage, petechiae and epistaxis | Drowsiness; ++++ Kernig sign; tender muscles; lumbar puncture showed 6 cells per cubic millimeter (normal spinal-fluid pressure). |

*Twelve additional cases in 7 states reported by Beeson and Hankey[31] — of 500 serum samples collected from patients with "benign aseptic meningitis," 24 were due to leptospira (12 of these to *Lept. canicola*). Clinical data available to authors meager. Most cases occurred in summer months, with clinical features resembling meningitides of viral origin. No hepatosplenomegaly present, and no patient had jaundice or leukocytosis. Spinal-fluid cell count seldom exceeded 300 per cubic millimeter; spinal-fluid protein usually elevated.

†Another case in New Orleans reported by same authors; no details given.

‡Negro patients.

Atlanta hospital during a two-year period. Of 500 paired serums from patients with meningitis collected in seven widely separated states, 24 were of leptospiral origin. Of these, 12 showed significant titers to *Lept. canicola*. The infection in dogs produces a profound interstitial nephritis that can progress from the acute stage to a subacute and chronic nephritis of a pyelonephritic pattern.[39]

TABLE 1. (*Concluded.*)

| AUTHOR | LIVER DYSFUNCTION | RENAL FINDINGS | THERAPY | SOURCE OF CONTACT | HIGHEST TITER | | REMARKS |
|---|---|---|---|---|---|---|---|
| | | | | | *Lept. icterohaemorrhagiae* | *Lept. canicola* | |
| Meyer et al.[8] | Definite icterus | Hemorrhagic nephritis | — | Icteric dogs | 1:30 | 1:300 | Diagnosis made in retrospect |
| Meyer et al.[6] | — | Leptospira isolated from urine on 32d day of illness | — | Patient worked in dog pound, annually handling over 150 dogs known to have leptospirosis | — | 1:10,000 | |
| Bruno et al.†[32] | Icteric index, 129 units; liver edge barely palpable; +++ test for bile in urine. | Blood urea nitrogen, 69 mg. per 100 cc. | — | — | 1:1000 | 1:10,000 | Patient had pneumonia |
| Tievsky and Schaefer[33] | No icterus | Moderate albuminuria; casts and white cells in sediment; blood urea nitrogen, 16 mg. per 100 cc. | — | None known | 1:100 | 1:10,100 | Patient cut foot 1 wk. before admission (no obvious sequelae) |
| Randall and Cooper[12] | In another case patient was owner of dog from which *Lept. canicola* (Strain B) isolated; had removed soiled newspapers from dog's quarters 11 days previously. | | | | | | |
| Rosenbaum[26] | Icteric index, 94 units; cephalin flocculation, ++. | No nephritis; leptospira found in urine on 16th to 29th hospital days; bile in urine. | Sulfadiazine and penicillin (no response) | Sick dog (had high titer for *Lept. canicola*) | 1:1000 | 1:100,000 | No central-nervous-system, renal or blood dysfunction |
| Molner et al.[27] | Direct contact with dogs in all cases. | | | | | | |
| Doerner and Hernandez[24] | Icteric index, 4 units; cephalin flocculation, ++++; thymol turbidity, 8-32 units; prothrombin, 100 per cent; total protein, 5.78 gm. per 100 cc. (normal albumin-globulin ratio). | Albuminuria, with red and white cells in sediment | Penicillin (gradual lysis) | Patient exposed to sick dog in camp 3-4 mo. before illness | 1:10 | 1:10,000 | Liver palpable only during stage of recovery; liver function normal 5 mo. after onset of illness. |
| Turrell and Hamburger[28] | Liver tender and enlarged; icteric index, 10-20 units; cephalin flocculation, negative on two occasions; total protein, 5.9 gm. per 100 cc.; total bilirubin, 2.3 mg. per 100 cc. | Blood urea nitrogen, 60 mg. per 100 cc. (early anuria occurred) | Penicillin (intramuscularly and intrathecally) for 18 days (rapid improvement) | Patient exposed to 2 sick dogs (swam with 1 in River) | 1:100 | 1:1000 | Early pneumonia (?); ecchymoses and gastric hemorrhage; significant muscle and liver biopsies. |
| Rosenberg[29] | Liver edge not palpable; icteric index, 21 units; bile in urine on 6th day; cephalin flocculation negative. | Albuminuria and cylindruria; blood urea nitrogen, 16 mg. per 100 cc. | — | — | 1:100 | 1:10,000 | Patient swam in river 6 days before illness; rapid, uncomplicated recovery; no significant leukocytosis. |
| Rosenberg[29] | No icterus; liver and spleen not palpable; bromsulfalein retention, 1 to 8 per cent; thymol turbidity, 5.6 to 11.6 units; cephalin flocculation, +++, ++++ and ++. | Numerous casts and white cells in sediment; red cells in urine on same day hemorrhagic herpes labialis appeared. | Penicillin in wax (300,000 units in single dose) on 2d day of illness; sulfonamide intravenously and orally for 14 days without effect. | Patient received minor dog bite 11 days before illness (hand healed without complications) | Negative to 1:10,000 | Negative to 1:100,000 | "Mild anicteric leptospiral hepatitis"; meningococcemia suspected on admission — epistaxis and myalgia prominent; prolonged convalescence. |

Leptospirae are never found in the glomeruli, which are normal, but apparently invade the tubules from the interstices. The resulting leptospiruria can continue for years.[6] McIntyre and Montgomery[39] have recently demonstrated that the locus of the cellular infiltrate is at the juxtamedullary zone and suggest that Trueta's shunt mechanism operates during the stage of leptospiral invasion of the kidney. The renal lesions of human leptospirosis are considered to be identical with the dog's interstitial nephritis,[40] and manifest themselves as poor concentration, transient albuminuria and cylindruria as well as hematuria and azotemia. Of the 2 fatal cases reported to date,[41, 42] an acute interstitial nephritis was present in each, and uremia was considered to be the cause of death. Molner[27] reported 1 fatal case without details.

The case presented by Turrell and Hamburger[28] and the case reported above are the only 2 in the world literature in which histologic study of the liver has been made during life. The biopsies in both cases were taken relatively late in the course of the period of jaundice (on the eighteenth and the thirty-first day of illness, respectively). Each patient showed mild hepatocellular damage consistent with a mild hepatitis.

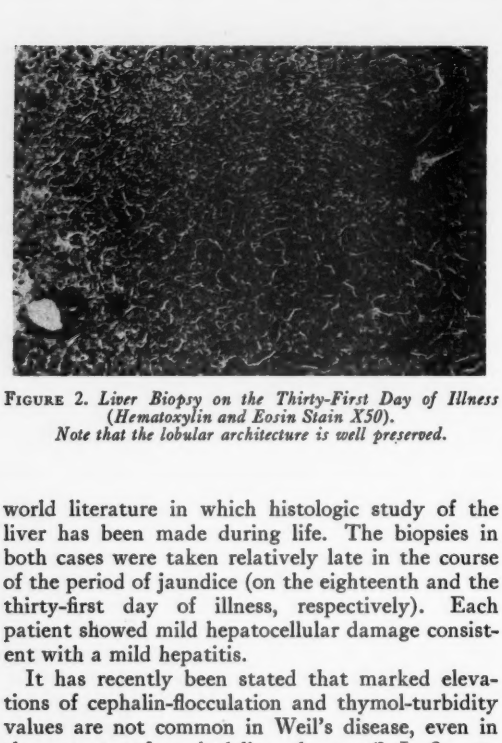

FIGURE 2. *Liver Biopsy on the Thirty-First Day of Illness (Hematoxylin and Eosin Stain X50). Note that the lobular architecture is well preserved.*

It has recently been stated that marked elevations of cephalin-flocculation and thymol-turbidity values are not common in Weil's disease, even in the presence of marked liver damage.[43] In 9 cases these tests were significantly lower than those in viral hepatitis at any level of hyperbilirubinemia. The reasons for this apparent discrepancy are not clear but illustrate that negative thymol turbidity and cephalin flocculation do not exclude parenchymal liver disease (Table 1).

Epistaxis, meningeal hemorrhage[44] and other hemorrhagic tendencies occur in the absence of liver damage and are presumably due to primary capillary damage.[45] Eye signs, including vitreous opacity and iridocyclitis, have been reported.[14, 46, 47]

The characteristic focal degenerative lesions in muscles as originally described in Weil's disease by Sheldon[48] have now been seen in canicola fever.[28] English workers have described erythema-nodosa-like skin lesions,[14] and alopecia has been reported.[49]

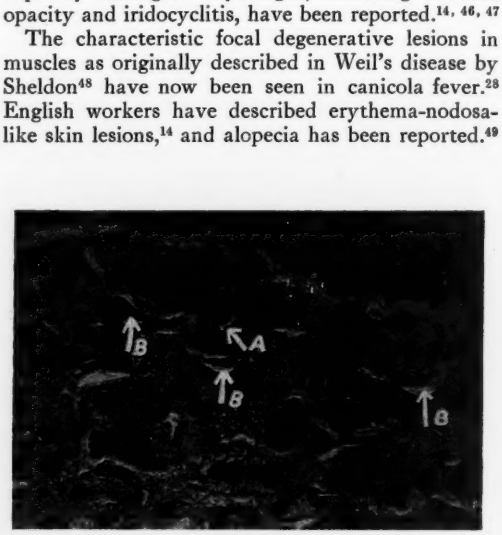


FIGURE 3. *Liver Biopsy (Hematoxylin and Eosin Stain X235). An inspissated bile thrombus is seen at* A. *Kupffer cells are filled with bile pigment* (B).

Serious complications, including myocarditis with transient heart block,[16, 18] paralyses[50] and psychoses[51] have been reported. Slow convalescence, with profound weakness, may persist for some time.

*Laboratory Findings*

Leukocytosis and secondary anemia are common, as in Weil's disease. However, it is well to stress the comment of Beeson and Hankey[31] that in the icteric forms and when the clinical picture is that of Weil's disease, there is nearly always a white-cell count of 12,000 to 25,000, whereas in the non-icteric and meningitic forms, the count is usually between 5000 and 8000.

The cerebrospinal fluid of the meningeal forms may initially display normal cell counts, which increase to levels up to several thousand.[8, 14] Polymorphonuclear leukocytes or lymphocytes may predominate.[14, 25, 28, 30]

Electrophoretic analysis of the serum proteins in a case of canicola fever with jaundice[11] showed elevation of all the globulin fractions on the fifteenth day. This is similar to the pattern found in a case of Weil's disease, in which the gamma globulin was increased and the alpha-2-globulin pronounced, possibly because of the severe febrile state.[52]

The diagnosis of canicola fever is established by the Schüffner agglutination lysis test for the presence of antibodies in the patient's serum.[35] Antibodies appear between the tenth and thirteenth days and reach their maximum in thirty days. A simple complement-fixation test designed for use

in laboratories doing routine Wassermann tests has been devised.[53] The leptospirae are ruptured by sonic vibration, yielding a very stable antigen of considerable specificity and sensitivity. Antibody formation may be detected before it is demonstrable by the usual microscopical agglutination test. Cross-agglutinations occur with other more common leptospiral species, but the significant antigen titer predominates. Over eighteen species of leptospirae have been reported to date.[54]

Infections with *Lept. ballum, bovis, grippotyphosa, sejroe, bataviae* and *saxkoebing* are rare and have been reported only in the European countries.[8, 55-58] An outbreak of central nervous-system disease due to *Lept. hebdomidis* (Strain B) has just been reported among American troops on Okinawa.[59] All followed water immersion; no patient had icterus. The first cases of human infection with *Lept. pomona* in the United States have recently been described.[60, 61]

Although direct culture methods are available,[35, 62] animal inoculation is better suited for demonstration of the spirochete. The Syrian hamster has been described as the best laboratory animal.[26, 32, 63] Death occurs by the tenth day after infection. Dark-field examination of the urine between the tenth and thirteenth days of illness may occasionally demonstrate leptospirae. Fresh urine with a neutral pH should be used.[45] Dark-field examination of the blood or spinal fluid is seldom rewarding and is not recommended.[31]

*Treatment*

Experience with the modern antibiotics in this disease has been negligible.

There has been some experience in the treatment of Weil's disease, but the variability of the clinical course of leptospiral infections makes adequate evaluation difficult. Antiserum for *Lept. icterohaemorrhagiae* has been used by Patterson[64] with some success in human beings. Penicillin has been of only partial value and has been used infrequently.[8, 14, 19, 24, 28, 64-67] Streptomycin was said to be of value in 1 case[44] and was effective in clearing the urinary-carrier state of hamsters and dogs infected with *Lept. canicola*.[68] Aureomycin was highly effective in experimental leptospirosis in hamsters.[69] Terramycin was strongly bacteriostatic in vitro and slightly superior in protecting hamsters from *Lept. canicola*.[70-72] Three cases of Weil's disease in human beings apparently responded to aureomycin,[73-75] and 1 to terramycin.[76] However, the largest study to date (67 cases of leptospirosis in human beings)[77] pointed out that in patients treated with chloramphenicol, aureomycin, terramycin, streptomycin or combined aureomycin with streptomycin, no apparent benefit was demonstrated. There was no effect on the prevention of jaundice or its duration, on reduction of central-nervous system symptoms or on the degree of renal involvement. Furthermore, the duration of the leptospiremia and persistence of the organism in the cerebrospinal fluid was not appreciably altered by any of the antibiotics employed. Leptospiruria was not studied.

## Summary

A case of *Leptospira canicola* (canicola fever) occurring in Connecticut is presented. The illness occurred five days after swimming in stagnant water.

A liver biopsy done on the thirty-first day of the disease showed mild, nonspecific hepatocellular damage.

There is considerable variance in the clinical manifestations of the disease in various parts of the world.

The disease is being reported with increasing frequency, and, although the incidence is evidently low, it should be stressed that occasional cases of hepatocellular disease and meningitides of undetermined etiology, probably due to the leptospiral organisms, are not being recognized.

The literature is reviewed, and all cases reported to date in the United States are outlined.

Since this report was submitted for publication, a new monograph by Gsell[78] has appeared, describing all the known clinical and laboratory data of the various strains of leptospira. Also, an outbreak of fever due to *Lept. canicola* in 9 members of one family has recently been reported.[79] All the patients had evidence of some liver involvement, although some were asymptomatic. Established contact was traced to a sick bulldog, which had probably contaminated the communal water dipper.

I am indebted to Dr. Paul Kunkel and Dr. George J. Friou for their assistance during the preparation of this report.

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# TUBERCULOUS MENINGITIS*

## Treatment of Spinal Block with Intrathecal Administration of Tuberculin

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ATLANTA, GEORGIA

THE treatment of spinal block occurring in tuberculous meningitis has been unsatisfactory. Recently, however, Smith[1-3] has reported successful results in such cases with the intrathecal administration of P. P. D. (Purified Protein Derivative). Two patients who were moribund and had failed to respond to streptomycin were treated with intrathecal administration of P. P. D. In both cases recovery ensued. This appeared to be complete after a year. A third case, in which the full decerebrate state had developed, was treated with intrathecal P. P. D., with temporary improvement. After a year's illness, the patient died, and at autopsy the exudate usually seen surrounding the brain stem in this disease was absent. This suggested that the effect of the P. P. D was to dissolve the exudate that had produced the block.

Subsequently, 19 patients have been treated with tuberculin intrathecally.[3] The results are summarized in Table 1.

Stimulated by the work of the Oxford group,[1] we have used this type of therapy on 1 patient, with gratifying results. The purpose of this paper is to confirm the previously reported results, to outline in some detail the method of treatment and to report the value of ventriculograms in demonstrating spinal block.

### CASE REPORT

A 24-year-old Negro truck driver was admitted to the hospital on September 11, 1950, with a diagnosis of miliary tuberculosis. X-ray examination of the chest revealed a left-sided, minimal pleural effusion and diffusely scattered minute, nodular densities throughout both lung fields, compatible with miliary tuberculosis. Gastric washings obtained on September 13, 14 and 15 were positive for tubercle bacilli by culture and animal inoculation. All subsequent gastric washings have been negative. The first-strength intradermal test with P. P. D. was positive, and repeat tests have remained so throughout the period of observation.

The patient was given 2 gm. of streptomycin intramuscularly and 12 gm. of para-aminosalicylic acid orally per day. At first, his course was stormy, with daily elevations of temperature. At the conclusion of 120 days of therapy, he had improved markedly, with complete clearing of the x-ray film of the chest and return of temperature to normal. However, 10 days later, an upper respiratory infection, frontal headache and stiff neck developed. Spinal tap revealed an initial pressure equivalent to 270 mm. of water, with 200 lymphocytes per cubic millimeter, a spinal-fluid sugar of 48 mg. per 100 cc. and a protein of 93 mg. per 100 cc. Smears and cultures for tubercle bacilli and other bacteria were negative.

Because of recent bacteriologic proof of miliary tuberculosis, therapy was reinstituted with 1 gm. of streptomycin intramuscularly and 12 gm. of para-aminosalicylic acid by mouth daily. The patient was also given weekly intrathecal injections of 50 mg. of streptomycin diluted with 10 cc. of physiologic saline solution. There was marked clinical improvement, with disappearance of all signs and symptoms of the disease. He was discharged on July 7, 1951, and was to be ambulated at home over a 6-month period with clinical evaluation at this hospital every 6 weeks. It is now evident that this course of therapy was inadequate.

Two weeks prior to the present admission the patient was found to be completely asymptomatic; however, 1 day later a frontal headache developed, gradually increasing in severity. He became disoriented 4 days before admission. Physical examination on October 5 revealed no papilledema, but he had a stiff neck, crusted lesions over the mouth, absent gag reflex, hyperactive left knee jerk and an equivocal Babinski sign on the right.

TABLE 1.

| INTERVAL OF OBSERVATION AFTER COMPLETION OF P. P. D. TREATMENT | TOTAL NO. OF CASES | ACTIVE AND IMPROVING CASES | DEAD OR DETERIORATING PATIENTS |
|---|---|---|---|
| *mo.* | | | |
| 6–8 | 3 | 3 | 0 |
| 9–14 | 7 | 4 | 3 |
| 15 and over | 12 | 7 | 5 |
| Totals | 22 | 14 | 8 |

The temperature was 101°F., the pulse 85, and the respirations 16; the blood pressure was 140/80.

Spinal puncture disclosed an initial pressure equivalent to 360 mm. of water. Dynamics were not free, suggesting partial block; after 10 cc. of spinal fluid had been removed, final pressure was equivalent to 140 mm. of water. Analysis of the fluid showed 220 white cells per cubic centimeter, with 96 per cent lymphocytes, and a sugar of 44 mg. and protein of 88 mg. per 100 cc. Neither tubercle bacilli nor other bacteria were isolated.

Two days after admission the patient had a generalized convulsion that lasted 5 minutes. After this, his optic disks were thought to be blurred. He showed progressive evidence of mental and physical deterioration, losing 14 pounds of body weight. He ran a febrile course, continuing to be anorexic and lethargic. Spinal puncture showed an increasing elevation in pressure and a slow, irregular fall after jugular compression, indicative of partial block. There was also a rise in spinal-fluid cells and total protein (Fig. 1).

Treatment consisted of 2 gm. of streptomycin intramuscularly daily for 14 days and then 1 gm. daily combined with 12 gm. of para-aminosalicylic acid by mouth until the 37th day of treatment, when the dose of para-aminosalicylic acid was increased to 20 gm. per day intravenously. Fifty mg. of streptomycin was given intrathecally 3 times weekly, all without any evidence of improvement. It was decided to use the method outlined by the Oxford group[1] before the patient became moribund.

On November 29, trephine openings were made in the skull approximately 2 cm. lateral to the midline and 2 cm. anterior to the frontal suture. The ventricular fluid was observed to be under moderately increased pressure. A ventriculogram (Fig. 2) demonstrated a block of the posterior fossa and moderate dilatation of the ventricular system. Intraventricular injections of P. P. D. were started on this date. A total of 5 doses was given as follows: 1st day (November 29), 0.000004 mg. of P. P. D. — left ventricle; 3d day

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(December 1), 0.000008 mg. of P. P. D. — left ventricle; 5th day (December 3), 0.000016 mg. of P. P. D. — right ventricle; 9th day (December 7), 0.000032 mg. of P. P. D. — left ventricle; and 14th day (December 12), 0.000064 mg. of P. P. D. — right ventricle.

The P. P. D. was administered into the ventricle through an 18-gauge lumbar-puncture needle. The procedure was done on the ward, with sterile technic. With each puncture, ventricular fluid was removed for study, and 50 mg. of streptomycin was injected into the ventricle along with the P. P. D. Streptomycin levels ranged from 11 to 15 microgm. per cubic centimeter in the ventricular fluid and from 7 to 10 microgm. per cubic centimeter in the spinal fluid. After each instillation of P. P. D. into the ventricles, the patient had a marked febrile response (as demonstrated in Figure 1) that returned to normal in 24 to 48 hours. This was accompanied by nausea, vomiting, lethargy and disorientation. These reactions were quite severe, and each successive one was more marked. Two days after the second injection of P. P. D., the spinal-fluid manometrics indicated relief of the block previously noted, and, 4 days after the third injection of P. P. D., ventriculograms showed a decrease in size of the lateral ventricles, with air in the cisterna magna and subarachnoid space, furnishing radiographic evidence that block no longer existed (Fig. 3).

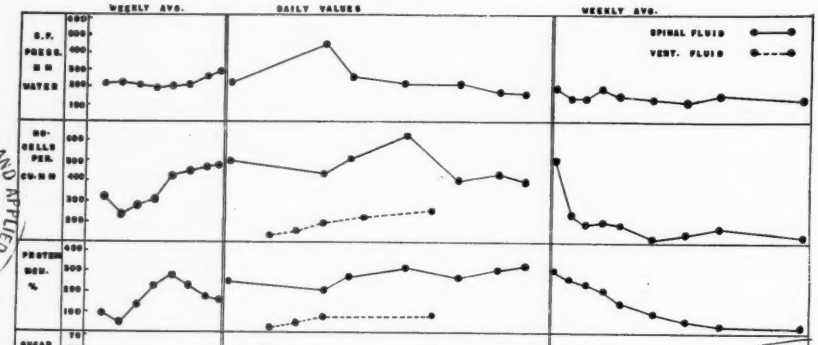


FIGURE 1. *Summary of Spinal-Fluid Studies and Temperature Curve.*

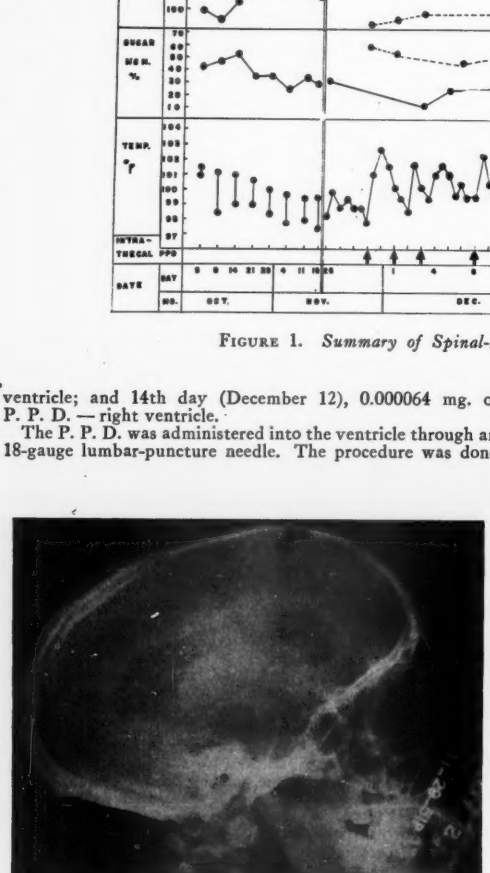

FIGURE 2. *Ventriculogram before Treatment, Demonstrating Block.*

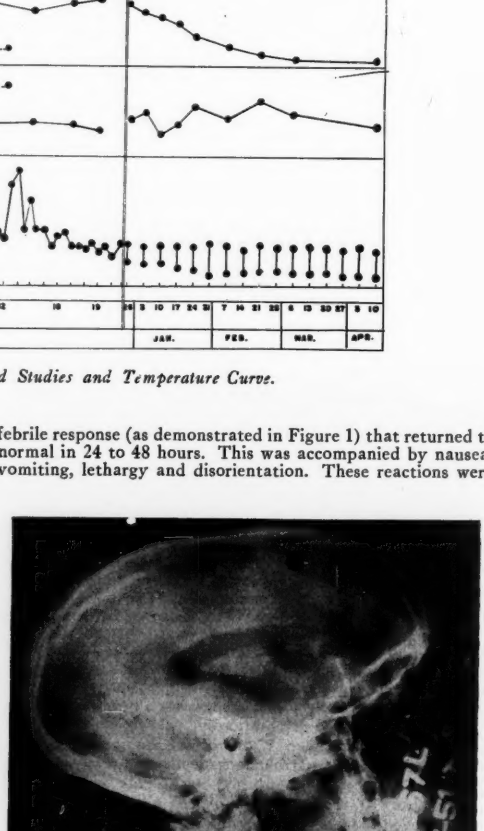

FIGURE 3. *Ventriculogram after Treatment, Demonstrating Relief of Block.*

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After the therapy had been completed, the patient's clinical response was dramatic. He became rational; the temperature became normal; the spinal-fluid pressure, cell count, protein and sugar returned to normal; and there were no remaining symptoms of active disease. The papilledema cleared, with complete return of vision. He gained 50 pounds. A summary of the temperature curve and spinal-fluid studies is presented in Figure 1. After 30 days of intravenous administration of para-aminosalicylic acid, the oral dose was resumed.

Throughout his illness the patient had persistent vertigo, which was thought to be due to streptomycin. This condition was greatly relieved by the use of 50 mg. of Dramamine orally every 4 hours while he was awake. On June 1, 1952, examination revealed no visual, auditory or vestibular impairment.

## Discussion

A nearly constant finding in fatal cases of tuberculous meningitis is the thick collar of exudate surrounding the midbrain.[1, 4, 5] Often, nests of organisms can be found embedded in the exudate. In this way, the tubercle bacilli are shielded from the action of streptomycin, both in the blood and in the spinal fluid.

There are striking changes in the spinal fluid of patients with tuberculous meningitis treated with intrathecal streptomycin. At the beginning of treatment, there is an increase in polymorphonuclear leukocytes and total protein, with a gradual decrease. It is thought that this reaction is due to tuberculin hypersensitivity since no marked polymorphonuclear reaction is produced when streptomycin is given intrathecally to a normal person or to patients with pyogenic meningitis.[1] Not only is there no significant response when streptomycin is given intrathecally to a person with a negative tuberculin skin test but also there is no response to the intrathecal administration of P. P. D. This suggests that the reaction is due to the liberation of the breakdown products of the tubercle bacilli.

In patients with positive tuberculin skin tests, there is a marked reaction similar to those observed in the case reported above (Fig. 1), with a sharp rise in the total protein and white cells; 40 to 80 per cent of the cells are polymorphonuclears, but, after several days, lymphocytes predominate. Cairns and Smith[2] believe that the response to intrathecal administration of P. P. D. is more than a chemical meningitis and is specific for a patient whose meninges are sensitized by either tubercle bacilli or their products. To achieve this reaction, the P. P. D. must be given intrathecally since, when it is given subcutaneously or intramuscularly, the reaction does not extend to the cerebrospinal pathways.

It is postulated that the spinal-canal block in this patient was broken by a fibrinolytic reaction evoked by the injection of P. P. D. into his sensitized ventricular system, which caused a localized response in the affected area. As demonstrated by Smith,[1] there is a transitory outpouring of leukocytes into the spinal fluid. It has been established[6] that polymorphonuclear leukocytes contain an enzyme, leukoprotease, capable of digesting proteins and of forming peptones and polypeptides, both of which are present in exudate. With the death of the polymorphonuclear leukocyte, the enzyme is liberated into the surrounding fluid. There is an antileukoprotease present in serum to inhibit its fibrinolytic action. When the cells pass into the cerebrospinal fluid, it is likely that these antienzymes are present in amounts too small to inhibit the leukoproteases released by the disintegrated leukocytes. Another enzyme, erepsin, present in the leukocytes, will break the polypeptides into free amino acids.[6] Perhaps these cells furnish enough enzymes to lyse the exudate causing the block. In this way, the tubercle bacilli that are usually buried in the lesion may be brought into contact with the streptomycin and thus may be more effectively destroyed.

A major problem is the duration of such intrathecal therapy. In this patient, the treatment was discontinued after the block was definitely relieved, as evidenced by ventriculograms and spinal-fluid manometric studies. Since trephines are done before intrathecal therapy with P. P. D. is instituted, we think it worth while to obtain ventriculograms. In this way, the block can be better localized and the therapy evaluated. It is recognized that this type of therapy may be dangerous and should be used very cautiously.

## Summary

The rationale for the use of intrathecal administration of P. P. D. and streptomycin in the treatment of spinal block due to tuberculous meningitis is discussed.

The gratifying response of a patient so treated is noted. This type of therapy should be seriously considered in similar cases of spinal block, although one should keep in mind the fact that this procedure may be dangerous.

Ventriculograms showed the block between the third and fourth ventricles before treatment and the absence of the block after treatment, and it is suggested that this procedure can be of considerable value in assessment of the results of treatment.

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# MEDICAL PROGRESS

## TUBERCULOSIS

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SO MANY articles have been written about tuberculosis in the past two years, and the subject is so complex, that it was decided to present this review from the standpoint not of the tuberculosis specialist but from that of the workers in other branches of medicine who might be interested in keeping abreast of the recent progress in this now particularly fascinating field. For this reason the main article is largely a statement of my own conclusions, and the comparatively short bibliography lists only articles in the standard, easily available journals.

The present attitude on the treatment of tuberculosis is a far cry from the days when it seemed important to have patients sit in "cure chairs" in snow drifts in Colorado. By 1920 there was already a shift of emphasis from outdoor living in the mountains to treatment by bed rest at any level. The cure, however, was being left to nature, with only feeble help from medical science. But a period was soon to follow when artificial rest was advocated and the diseased lung was deliberately "compressed" by pneumothorax, or thoracoplasty. This was a step in advance, but one dared not dream of the situation that prevails today, when treatment includes drugs that have been proved highly effective in clearing the pulmonary infiltrations of tuberculosis and surgical procedures that allow the removal of necrotic tuberculous foci almost as if rotten spots were being cut from an apple. But such statements make the problem sound too simple. In the first place, chemotherapy is a complicated problem involving toxicity, dosage and duration of treatment, and particularly the combining of drugs to prevent the resistance that has so far invariably occurred when a single drug is used. Then there is the relation of chemotherapy to surgery, and the relation of rest to both chemotherapy and surgery. And just now confusion has been confounded by premature publicity concerning a promising new drug — isoniazid. So after being banished to the woods, far from medical centers, the problems involved in the treatment of tuberculosis are returning to the medical schools and are beginning to interest the best brains of the physicians, surgeons, pharmacologists, bacteriologists and roentgenologists.

### DECLINE IN DEATH RATE

It is hard to know whether to give the credit to natural epidemiologic trends, better living conditions, health education, isolation procedures, sanatorium care, chemotherapy or surgery, but the morbidity and mortality curves continue to fall.

In the registration area of the United States the death rate from all forms of tuberculosis in 1900 was 202 per 100,000 population. In 1945 it was 40; in 1948 it was 30; in 1950 it showed a remarkable drop to 22.2; and the 1951 provisional rate is given by Mary Dempsey, statistician for the National Tuberculosis Association, as 20.1. There were actually 30,837 deaths from tuberculosis in the United States in the year 1951: 118,438 new cases were reported during that year. "Mass case-finding surveys" show 1 or 2 active cases per 1000 adults given x-ray examinations. It is estimated that altogether there are about 400,000 cases of active tuberculosis in the United States at the present time, and 800,000 inactive cases.

In Massachusetts the death rate in 1900 was 253; it was 29.6 in 1948 and 18.7 in 1951. In Massachusetts in 1951, 2656 new cases of pulmonary tuberculosis were reported.

### TODAY'S PROBLEMS

Whatever the ultimate decision, the primary interest today is in chemotherapy: the benefits derived from the use of streptomycin and para-aminosalicylic acid, the promise of new drugs and combinations of drugs, and the relation of chemotherapy to rest and surgery. Running a close second in interest is surgical excision of active tuberculous foci: the choice between resection and the time-honored thoracoplasty, and again the relation of chemotherapy and rest to surgery.

### A METHOD OF EVALUATING RESULTS

Not only are new methods of treatment available, but also, in the past six years, large-scale methods of evaluating the results of treatment have been developed. The plan has been to pool the experience of large numbers of hospitals. Three great organizations have conducted such programs: the Veterans Administration with the Army and Navy; the American Trudeau Society (Medical Section of the National Tuberculosis Association); and the United States Public Health Service. In some instances the scheme has been carried to the ultimate, and medicine is practiced by central-office protocol to an astounding degree. Such a scheme is the following. A certain list of hospitals agrees to co-operate in the study of the use of certain drugs or combinations of

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drugs. A central office draws up protocols for the use of these drugs, describing a list of regimens, including control groups. The individual hospital submits to the central office a list of the names of patients who are to be included in the study. The central office "randomizes" the cases on the various regimens and writes a letter to the hospital telling who is to get what. The randomization may be done in different ways — for instance, patients whose army serial numbers end in 1, 2 or 3 may be placed on regimen No. 1; those with 4, 5 and 6 will be on regimen No. 2 and so forth. Then, each month, the hospital sends to the central office a report that includes an x-ray film and data on sputum or gastric smears and cultures. (Many other details may be included in the reports at different times.) Then, at certain intervals, an unprejudiced board, which knows nothing about the patient or his treatment, evaluates the x-ray films and decides which of the films taken in series show stability, or progression, or regression in different degrees. Then the statisticians go to work, and one has *an* answer, though there are many factors coming into a study conducted in this way that make one wonder if it is *the* answer.

It should be stated here that most of the studies, including the widely publicized ones of the Veterans Administration, have not been conducted along such purely statistical lines. But the study of statistics, and how to collect them and interpret them, has assumed a new prominence in the treatment of tuberculosis.

### Dependence on X-Ray Examination

Statistical studies, as outlined above, call attention to the extreme dependence now being placed on the x-ray film.

Most of the decisions about how a patient should be treated are made at conferences in which a number of doctors are grouped around a bank of x-ray illuminators and are polled after the manner of a well conducted democracy regarding their opinion of how to treat the x-ray film. Many of the doctors whose votes determine the course to be followed have never seen the patient. This statement has a distressing sound, but it is nevertheless true that physicians depend on the x-ray film more than on any other one thing and that the course to be followed usually depends on x-ray shadows and the changes that occur in them. Of particular importance is the evidence for or against the presence of cavities. This matter is mentioned below in the discussion of surgical procedures.

Increased use is being made of tomograms (planigrams, laminagrams) to determine the presence of a cavity. This special technic, by means of which a sharp image is obtained at specific levels in the lung whereas the shadows of the remainder of the lung are blurred, is particularly useful in bringing out cavities in the area behind the clavicle and first rib. However, even with a tomogram there are frequent differences of opinion about the presence of a cavity.

The difficulties in x-ray interpretation are not limited to the study of tomograms. There is often a disagreement among roentgenologists regarding whether ordinary films taken in series show progression of the disease in a particular case. It is also true that the same man confronted at a later date by the same pair of films may contradict himself about the changes that have taken place. Fortunately, such disagreements are usually on minor changes, but a long period of hospital care often depends on whether the x-ray film is interpreted to show a spread of the disease.

### The Tubercle Bacillus

In recent studies the success of a given treatment has been judged by two things: the x-ray change; and the presence or absence of tubercle bacilli. The x-ray problem having been discussed, some interesting developments in the field of bacteriology come up for consideration.

The first of the new "discoveries" is that acid-fast bacilli, which are readily demonstrated in stained smears, may not grow on culture or produce disease in laboratory animals. This finding has been so frequently confirmed in the best laboratories that the bacteriologist is now called upon to decide whether such organisms are living, "sleeping" or dead.

Attention has recently been focussed on this problem because of discussions regarding the effect of chemotherapeutic agents on the tubercle bacillus, but another factor besides chemotherapy seems to influence the ability of the organisms to grow. This factor is whether the bacilli are in an open cavity or a closed cavity, and whether there is free bronchial communication or an essentially closed bronchus. Even without chemotherapy it is often impossible to grow tubercle bacilli obtained from caseous material in an undrained cavity, and after extensive chemotherapy it may still be possible to grow the bacilli obtained from open cavities in surgical specimens.

### Chemotherapy in General

The whole face of the tuberculosis problem was changed when in 1945 it began to be appreciated that a new antibiotic, streptomycin, would exert a favorable effect on tuberculous infection in human beings. Since that time many other such agents have been tried and certain synthetic compounds have also proved their value. Innumerable problems have therefore arisen regarding the chemotherapy of tuberculosis and its relation to the previously accepted treatment by rest, compression and excision.

One has first to consider just what chemotherapy can be expected to accomplish. In the original

study of any case a target should be selected and chemotherapy should be given its proper place in the over-all plan and not tried indiscriminately. For instance, it has seemed unlikely that streptomycin could "cure" extensive bilateral disease with large cavities embedded in fibrous tissue, and because of the problems of toxicity and resistance involved, streptomycin has often been withheld. On the other hand, if there is a single thin-walled cavity in the midst of what appears to be exudative disease, streptomycin may be expected to expedite the clearing of the exudate with a disappearance of the cavity. But in the original planning such a result should not be considered a certainty, and if a review at the end of six months shows the cavity still present, surgical measures should be considered. So the original effort must be to fit chemotherapy intelligently into an over-all plan.

Without at the moment taking up problems of dosage and duration of treatment the recent trend toward prolonged treatment should be emphasized in these general remarks on chemotherapy. The original program was for an arbitrary four months. Because of toxicity and resistance the time was shortened to six weeks. But when it was found that smaller doses reduced the toxicity, and the combination of streptomycin and para-aminosalicylic acid markedly delayed the development of the resistance of the tubercle bacilli to streptomycin, longer treatment periods were again instituted. At present eight months is almost a minimum, and one and a half or two years of treatment is not unusual.

Another factor of primary importance in the chemotherapy of tuberculosis is that of the use of drugs in combination. It has already been intimated that PAS added to streptomycin has changed the whole problem of resistance, which is so important in the treatment of a chronic infection like tuberculosis. It is now an almost accepted fact that if a single drug is used to treat tuberculous infection the tubercle bacilli will soon develop a resistance to it. It is this phase of the problem that has aroused so much interest in the "new drug" — isoniazid, the use of which is discussed below.

## Compression Therapy

It seems like a return to a forgotten past to mention compression therapy and particularly artificial pneumothorax. But in spite of their drawbacks compression methods have a place and should still be considered as possibilities in an over-all plan.

### *Pneumothorax*

Artificial pneumothorax was once a popular treatment for pulmonary tuberculosis, and was used not so many years ago in about 40 per cent of sanatorium patients. However, it is rapidly falling into the discard, partly because of the dread of the tuberculous empyema that all too frequently accompanied it and partly because of present dependence on chemotherapy. But there are those who still believe that it is a useful procedure in carefully selected cases and that streptomycin coverage may help to prevent empyema.

### *Pneumoperitoneum*

There is little new evidence of the effectiveness of this form of therapy. Statistical proof of its value is particularly hard to get since most patients treated in this way are also receiving chemotherapy. The best results seem to be in acute bilateral exudative disease with or without cavities. The combination of pneumoperitoneum and temporary phrenic-nerve paralysis is still useful in certain cases with lower-lobe cavity.

### *Thoracoplasty*

There are several recent articles concerning the end results after a standard thoracoplasty. In general, these results are good, but therapy conferences are still filled with discussions of when to do thoracoplasty and when to resect, with the recent trend toward resection, often with a modified thoracoplasty in addition. Several surgeons are performing the resection and thoracoplasty at the same operation. So far, the results seem satisfactory, and the patient is spared a second operation. In general, there is no question of the value of thoracoplasty and little likelihood of its complete replacement by resection, but the trend to cut out the rotten spots instead of compressing them by deforming operations on the thoracic cage is bound to continue.

### *Extraperiosteal Plombage*

A now popular operation consists in stripping the periosteal layer from the undersurface of the ribs, leaving the ribs in place and then packing lucite balls or fiber glass between this surface and the ribs. In this way a new layer of periosteum is allowed to form at a low level, and a permanent collapse of the apex of the lung is achieved. Some surgeons leave the balls in permanently; others remove them after a few weeks and do a modified thoracoplasty, leaving the first rib in place. These extraperiosteal procedures, which are usually chosen when only a small amount of collapse seems necessary or when the patient is in poor general condition, have certain distinct advantages over the old extrapleural procedures.

## Surgical Excision

The discussion so far must have made it evident that through the years attention has turned more and more to the possibility of the surgical removal of treacherous tuberculous foci. As thoracic surgery and better methods of anesthesia developed, this question was often raised. The early objections were that, no matter what was removed, active tuberculous tissue would certainly be left behind, and

further that if the surgeon's knife should cut across an active tuberculous lesion a permanent draining sinus would probably result. But as more lung "tumors" were resected it was found that many of them were not new growths but sharply circumscribed areas of caseous tuberculosis that were called tuberculomas. And even without the streptomycin protection that later became available most of these patients did well after operation and had no recurrence of active tuberculosis. By 1942 reports on 80 resections for tuberculosis had accumulated in the literature, 30 of them having been undertaken because of an erroneous preoperative diagnosis of new growth. Then, in 1943, Churchill and Klopstock reported 6 cases of planned lobectomies for tuberculous lesions of a different sort, most of them single cavities with little surrounding infection, or diffuse tuberculous infection of the bronchi. Encouraged by this report Sweet started a series of lobectomies and pneumonectomies in which he broadened the indications to include irreversible bronchostenosis, lower-lobe disease, thoracoplasty failure and an essentially destroyed lung when the other lung appeared normal. But there were so many late deaths in this and other series that the interest in such operations began to wane. Then came streptomycin, and a renewed interest in resection has swept the world, so that in the journals published in the years 1950 and 1951 there are reports on roughly 3800 pulmonary resections for tuberculosis, of which 800 were lobectomies, 1300 pneumonectomies, 300 segmental or wedge resections and 1400 unclassified.

Of paramount interest in this change of attitude is the part played by streptomycin. It was soon found that this drug prevented the early and late spreads that had been so much feared. But a new difficulty arose in the shape of postoperative bronchial fistulas, with or without empyema. And, strangely enough, some surgeons were blaming these complications on the streptomycin itself. They agreed that short preoperative and postoperative courses of streptomycin prevented spreads but maintained that prolonged preoperative chemotherapy led to a higher incidence of fistula and empyema. This discussion still goes on but has been somewhat quieted by the finding that the combination of streptomycin and PAS gives better results than streptomycin alone, and that really prolonged preoperative chemotherapy will usually remove the hazard of viable tubercle bacilli in the field of operation.

Finally, there came the fascinating "Sunmount concept" (Dr. Nicholas D'Esopo, of the Veterans Administration Hospital, Tupper Lake, New York), that perhaps the way to treat pulmonary tuberculosis was to keep up chemotherapy as long as the x-ray film showed clearing of the process, and then to have the surgeon resect the treacherous residua foci, and so get rid of the disease once and for all. This "pilot study" was aided by Medlar, a pathologist with an unusual knowledge of tuberculous infection. He found that almost without exception the surgical specimens (lobes, segments or wedges) given to him for examination, no matter how long the period of chemotherapy, had necrotic centers that connected with a bronchus and were therefore considered dangerous. But at this point he discovered the bacteriologic fact noted above of bacilli that were evident in stained smears but would not grow. So a new problem arose regarding whether there was any need for the surgical removal of lesions harboring only "dead" tubercle bacilli. This problem is still unsettled.

There are other questions concerning the relation of chemotherapy to surgery, such as what type of lesion requires streptomycin protection, and how long a preoperative and postoperative course of chemotherapy is required for the different types of disease. The trend is certainly toward prolonged therapy both before and after excision, but there is much to be learned.

## Rest

One feels like a heretic to question the importance of rest in the modern treatment of tuberculosis. Very often chemotherapy and surgery are spoken of as auxiliary treatments to the backbone of therapy, which is assumed to be bed rest. This may well be, but granted that bed rest is essential for the patient with fever or toxic symptoms, how long is it necessary to continue this rest for the patient who has no symptoms and is on prolonged chemotherapy? How much can the period of bed rest be shortened by chemotherapy? How long should ambulatory therapy be continued in the sanatorium? And how soon will the time come when chemotherapy can safely be continued on an outpatient basis? These questions are clamoring for a solution, but the answer is not yet available. Several studies are in progress. Likewise there arises the question of rest as it relates to surgery, particularly how much bed rest is necessary after resection. If one assumes that all the grossly active lesions have been removed, and if the patient is on postoperative chemotherapy, how long should he be kept in bed? Most institutions insist on a long postoperative bed-rest period. Are they overdoing it, or should one insist on playing safe?

## Streptomycin and PAS

In chemotherapy streptomycin still holds first place, and the early dreads of toxicity (shown by vertigo) and the development of tubercle bacilli resistant to streptomycin have largely been dispelled by a reduction in the dosage of this drug and its combination with para-aminosalicylic acid. The present preferred regimen is 1 gm. of streptomycin sulfate intramuscularly twice a week and 12 gm. of para-aminosalicylic acid by mouth

daily. This combined, intermittent schedule, which is effective and of low toxicity, prevents to a high degree the development of resistance to both drugs.

So far it has been assumed that streptomycin twice a week is as good as daily streptomycin, and the long and complicated tables of the Veterans Administration, Army and Navy study seem to justify that conclusion. However, there are some who still hold that the daily treatment is better, particularly for bronchial lesions, and there is a recent trend toward daily streptomycin for the first month and then twice a week. However, all factors (toxicity, resistance and so forth) considered, the twice-a-week regimen seems the best standard treatment.

The Veterans Administration investigators have committed themselves to streptomycin sulfate as the drug of choice, but there are still many who prefer dihydrostreptomycin, which the drug companies are producing in large amounts.

The criticism of dihydrostreptomycin is that it may promote deafness, but some claim that the deafness occurs only with dihydrostreptomycin *hydrochloride* (not sulfate) and only when doses of 2 or 3 gm. are used, or when the sulfate is used for long periods. For present prolonged treatment the regular streptomycin is probably the drug of choice except in patients who have become sensitized to it.

Whatever combination of drugs proves most useful in the future, there is today a definite trend toward prolongation of treatment. Eight months (instead of four) is becoming the average course, and much longer courses are common. Unless cavities persist, almost 100 per cent of cases have negative cultures for tubercle bacilli at the end of eight months. If cavities are still present at this time (or even earlier) some surgical procedure should usually be instituted. If the extent of the disease contraindicates surgery the hope is raised by certain investigators that prolonged chemotherapy may yet "sterilize" even fibrocavernous lesions. However, it seems unlikely that any drug will cause tubercle bacilli to disappear permanently from such foci.

Repeated or interval treatment by chemotherapy is usually frowned upon. It is now believed that, once started, the drugs should be continued until maximum benefit has been obtained. If the drug is stopped and a relapse occurs, retreatment is usually not as successful as initial treatment. Therefore, before drug therapy (or any therapy) is begun, the case must be carefully evaluated and a long-range plan evolved.

Another problem concerns chemotherapy for the case that has become resistant to streptomycin. There are patients who become worse during treatment and are then shown to have resistant tubercle bacilli. In such cases it is usually best not to continue streptomycin. And it is partly for them that the search for new drugs has been kept up. However, there is often continued improvement if the combined use of streptomycin and PAS is carried on. The explanation in such cases may be that an individual patient harbors both streptomycin-resistant and streptomycin-sensitive organisms in the same or in separated areas, and that bacteriostasis of the sensitive bacilli may still be going on. The use of Viomycin and other drugs in resistant cases is discussed below.

There are three types of tuberculous infection that in the early years of streptomycin study were considered as not needing chemotherapy because they had in the past responded so well to no special treatment or to bed rest. These three are minimal pulmonary tuberculosis, tuberculous pleurisy with effusion and "childhood" infection. There is now a trend toward treating all cases of active tuberculous infection by chemotherapy because the outcome of rest treatment for any type of disease has never been predictable and temporary relapses have occurred in perhaps 30 per cent of the cases even with the best prognosis.

If, then, one accepts prolonged, combined, intermittent chemotherapy as the regimen of choice, what may be expected from it? It is too early to talk of the effect on mortality. It is true that in Veterans Administration hospitals the previous death rate of about 20 per cent of all admissions has been reduced in recent years to about 10 per cent, but one cannot say for sure how much of this is due to chemotherapy in general or to any particular kind of chemotherapy. So far as improvement in the x-ray picture is concerned, the combined therapy (in the Veterans Administration study) gives marked or moderate improvement in about 50 per cent of the cases after four months of treatment and about 70 per cent in eight months; 70 per cent of all patients treated had negative sputum or gastric cultures at the end of eight months.

### Isoniazid

A new drug appeared unexpectedly and prematurely in February, 1952. This drug is isonicotinic acid hydrazide with its name usually shortened to "isoniazid." It is distributed by several companies, each of which has its own trade name. It is easily manufactured, is effective in small doses, can be taken by mouth and is apparently of low toxicity. It is extremely effective in the test tube and in laboratory animals, and has relieved symptoms in large numbers of patients. Unfortunately, it has so far not led to the x-ray improvement that might have been expected; sputum conversion has been disappointingly low, and when the drug is used alone, there is increasing evidence of early development of resistance. Several studies have shown that this resistance appears in over half the cases in less than three months. Some think that this laboratory finding does not necessarily mean that the drug has lost its beneficial effect on the patient.

This development of resistance points again to the necessity of using drugs in combination. It is now hoped that isoniazid will take the place of PAS combined with streptomycin. If it is as effective as PAS in delaying the development of resistance it should have two added advantages: the avoidance of the gastrointestinal disturbances so common with PAS; and an additional bacteriostatic effect of its own, which is not possessed by PAS.

It should be noted that at this writing a large proportion of the patients selected for treatment have not been of the sort to give any new drug a fair trial since they have often been persons with far-advanced disease who have already had prolonged ineffectual chemotherapy and are most probably streptomycin resistant. But there are an increasing number of patients with early disease who are taking isoniazid, and recent reports on this group seem to show results almost as good as those that formerly occurred with streptomycin alone.

The most effective dosage of isoniazid has not yet been determined. Trial doses so far range from 150 to 300 mg. per day, with a trend toward the larger doses. In some studies the dose is calculated on the basis of 3 to 5 mg. per kilogram of body weight.

## Other Drugs

*Marsilid (1-Isonicotinyl-2-Isopropyl Hydrazine)*

This drug was used in the early studies with isoniazid (isonicotinic acid hydrazide). In recent clinical studies little use is being made of marsilid because of apparently greater toxicity and no greater therapeutic effect.

*Pyrazinamide (Aldinamide)*

Just before isoniazid made its appearance, much interest was aroused by early reports on the use of this drug. There was striking clinical and x-ray improvement, but unfortunately early development of resistance with later clinical relapse. The interest has now swung almost completely from aldinamide to isoniazid.

*Viomycin*

Some months before the appearance of isoniazid, attention was focussed on this antibiotic as a possible alternative for streptomycin in streptomycin-resistant cases. It was shown to be highly effective in laboratory animals and in special cases in human beings. However, the toxic dangers, particularly in changing serum electrolytes and in causing vertigo and deafness, seemed apparent, and at the moment interest has waned. It may be revived if the "new drugs" do not live up to expectations.

*Tibione*

This is now rated as a "third-class drug" and is no longer employed.

*Neomycin*

This drug is on the black list because of the great danger of deafness.

*Mycomycin*

This antibiotic is unstable, and attempts to produce a purified drug have resulted in almost complete loss of the original striking effects observed in laboratory animals.

*Streptokinase*

This drug has been used largely in nontuberculous infection, but recently many trials have been made to determine if it would break down the thick exudate of tuberculous meningitis and tuberculous empyema and allow better penetration of chemotherapeutic agents. The results have not been completely satisfactory, but they warrant further trial.

## Tuberculous Meningitis

The surest proof of the value of streptomycin in the treatment of tuberculous infection has been the "cure" of a fair percentage of cases of tuberculous meningitis, a disease that was previously considered 100 per cent fatal. There is therefore a keen interest in the follow-up study of patients with meningitis who were started on streptomycin several years ago. It is becoming increasingly difficult to get satisfactory figures because of changes in treatment and because the figures on miliary tuberculosis without meningitis are often mixed with those on the much more serious meningeal conditions.

The Veterans Administration series reported in January, 1951, shows that of 80 patients with meningitis (without miliary disease) who were checked at the end of twenty-four months only 11 per cent were living. The figures presented in January, 1952, are somewhat confusing but show a definite improvement. Perhaps this is because in later years PAS was added to the routine streptomycin treatment.

In her classic series in children Dr. Edith Lincoln has used Promizole rather than PAS and reports 2 survivals in every 3 cases. She believes that Promizole is better for her long course of two or more years of treatment. There is hope that isoniazid will be better than either PAS or Promizole.

The use of streptokinase to break down the thickened exudate of tuberculous meningitis has been mentioned. In England the intrathecal injection of tuberculin is being used for the same purpose. The British reports are encouraging, but in this country the dangers of such treatment have led to caution in its administration.

## Special Studies

*Bronchoscopy*

For the benefit of those not familiar with the procedures used in tuberculosis sanatoriums it may be

worth while to call attention to the fact that bronchoscopy has almost become part of the routine examination of patients. The presence of tuberculous infection of the bronchial mucous membrane greatly influences the decision about chemotherapy, pneumothorax, thoracoplasty or excision. Such an infection occurs in mild or moderate degree much more frequently than was previously supposed. Unfortunately, it is often present only in the smaller bronchi, where it cannot be seen with the bronchoscope. As a rule, bronchial tuberculosis responds favorably to streptomycin treatment, and some observers believe that treatment daily, and not twice a week, is necessary in such cases.

*Test for Respiratory Function*

This phase of the modern study of a tuberculous patient must be passed over quickly in this review, even though it is claiming more and more attention from the physicians and surgeons who are planning treatment. The number of possible physiologic tests is infinite, but their application to clinical decisions is difficult. The main practical use of the tests is to help in deciding whether a given patient has sufficient respiratory reserve to stand a specified surgical procedure such as the removal of one lung. The percentage of cases now being studied in which the decision actually depends on the tests is probably small, but much is being learned about pulmonary physiology.

*Studies of Bone Marrow and Liver*

Generalized tuberculous infection is being recognized more often than formerly. This is particularly true in older patients who enter the hospital because of unexplained fevers. Sometimes, a puncture of the bone marrow or liver will result in the recovery of tubercle bacilli and establish the diagnosis. These studies are mentioned as an interesting trend and not as a recommendation for routine use. Sometimes, the finding of acid-fast bacilli on smear, without a check by guinea pig or culture, leads to a false conclusion.

## ACTH and Cortisone

There has been much discussion of the effect of these drugs on tuberculous infection in laboratory animals and in human beings. The present knowledge is best summarized in the reports of committees of the American Trudeau Society published in the August, 1952, issue of the *American Review of Tuberculosis*.

### The Committee on Therapy reports:

In the analysis of the 81 cases, it is obvious that exacerbation of tuberculous infection does not inevitably result from treatment with cortisone or corticotropin. On the other hand, it seems clearly demonstrated that hormone therapy may have a devastating effect on active or apparently inactive tuberculosis. This was particularly apparent in the cases coming to autopsy. Often there was a marked and even spectacular dissemination of the disease, and the observation was repeatedly made that tubercles were poorly walled off and contained numerous tubercle bacilli.

### The Committee on Medical Research reports:

1. The administration of cortisone or corticotropin to animals with experimental tuberculosis may produce a variety of effects, depending on the species of animal and the experimental conditions.
2. The hormones produce a lessened reactivity of the small blood vessels, which, in turn, causes a reduction in the inflammatory response of sensitized tissue to the tubercle bacillus.
3. Cortisone can convert a chronic smoldering tuberculous infection in mice into an acute progressive process.
4. When the adrenal hormones are withdrawn, there may be a sudden flare-up of tuberculous disease.
5. The hormones have no significant action on the tubercle bacillus or tuberculin in vitro.

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# MEDICAL INTELLIGENCE

## HICCUPS COMPLICATING MYOCARDIAL INFARCTION*

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HICCUPS occurring with acute myocardial infarction indicate an extremely grave prognosis.[1] It has been said that all patients afflicted with this distressing complication die, but the clinician will find little published information on the subject.

This complication was first described by Weiss[2] in 1939. No other articles appeared until 1951, when Rubin et al.[3] reported a case of myocardial infarction with hiccups that responded to left-phrenic-nerve crush after other measures, including quinidine, had failed.

There is considerable information about postoperative and postencephalitic hiccups. However, the very number of divergent treatments indicates the need for further investigation of this problem. Bailey[4] believed that drugs were not effective and that the following approach should be used in the management of postoperative hiccups: one should relieve gastric distention, rule out uremia and pleurisy, and then use 100 per cent carbon dioxide through a mask to the point of discomfort (this, of course, is not possible in myocardial infarction). As a last resort, the left phrenic nerve should be tied and injected. Since the publication of his report, Bellet and Nadler[5] have shown that quinidine is of value in some cases. Jirasek,[6] in 1925, stated that bilateral phrenic-nerve crush is a harmless procedure in patients who do not have exclusively abdominal respiration. This procedure has been reported in a number of cases as a method of treating singultus not complicating myocardial infarction, the largest number of cases being in Skillern's[7] group. In 1931 he treated 4 cases of postencephalitic diaphragmatic tic by bilateral resection of the phrenic nerves. This treatment was successful after the usual methods had failed.

We have seen 2 patients with myocardial infarction with hiccups who have lived and returned to their occupations. Both were treated by bilateral phrenic-nerve crush, after other measures failed, and neither patient experienced orthopnea or dyspnea after paralysis of both diaphragmatic leaves.

### CASE REPORTS

CASE 1. H. T., a 68-year-old man (a mesomorph), was admitted to the hospital on August 29, 1950, for repair of bilateral inguinal hernias. On the following day a bilateral herniorrhaphy was performed under spinal anesthesia, and the patient was returned to the floor in good condition. Two days after admission he complained of hiccups, and the usual treatments for singultus were employed, with only transitory success.

During the morning of September 1, he experienced a sudden onset of pain in the right anterior portion of the chest. Because of this and the persistence of singultus, one of us was asked to see him. Examination showed a slight fever, elevated pulse rate and suppressed breath sounds at the left base, posteriorly, and slight increase in tactile fremitus at the posterior right base. An electrocardiogram (Fig. 1) was compatible with a diagnosis of recent posterior myocardial infarction. Serial electrocardiograms, temperature curve, leukocyte counts and sedimentation-rate determinations were also compatible with this diagnosis. The patient received the usual treatment for myocardial infarction, which included Dicumarol. The singultus remained intractable, continuing even when he was asleep, despite oral and intramuscular administration of quinidine, intravenous injection of procaine, morphine sulfate, a Levine tube, an abdominal binder and sedation. The chest pain soon left, but the course was rapidly downhill, with frequent vomiting. Finally, phrenic-nerve crush was decided on. Fluoroscopy showed that both

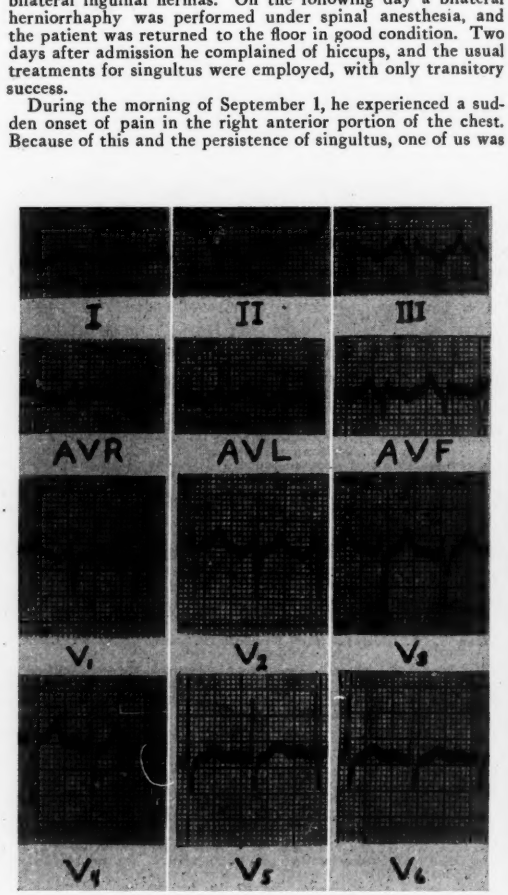


FIGURE 1. *Electrocardiogram in Case 1.*

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leaves of the diaphragm were involved, and hence both phrenic nerves were blocked in two stages. The blocks were shown to be successful, by fluoroscopy, and the patient remained comfortable for about 8 hours; then diaphragmatic function and singultus recurred. A left phrenic-nerve crush was done and seemed to lessen the intensity of the hiccups. Three days later the right phrenic nerve was crushed. Singultus disappeared, and the patient showed no respiratory embarrassment. Approximately 1 week later he had several short, transient episodes of singultus involving accessory muscles. Quinidine was given, the oxygen was discontinued, and he had no more hiccups.

He gradually recovered and was asymptomatic on discharge on October 27. He was seen again on December 5, when he had no complaints and the electrocardiogram was compatible with an old posterior myocardial infarction. He returned to work, as a watchman, on January 1, 1951, and continued to work until March, 1952, when he died suddenly. Permission for post-mortem examination was not obtained. An electrocardiogram in October, 1951, showed no changes with the exception of less marked Q waves in Leads 3 and AVF.

Case 2. F. C., a 58-year-old man (an endomesomorph), was admitted to the hospital on February 6, 1952. Several hours prior to admission he had noted severe substernal pain radiating to both shoulders and down the medial aspect of the left arm. This was accompanied by dyspnea. Serial

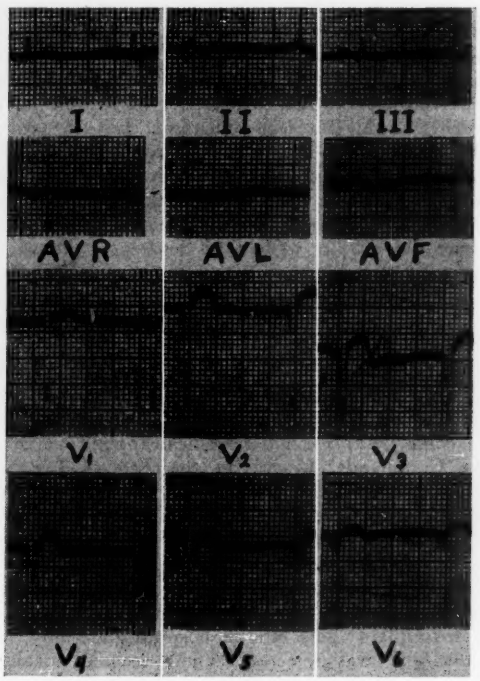


Figure 2. *Electrocardiogram in Case 2.*

electrocardiograms, temperature curve, leukocyte counts and erythrocyte sedimentation rates were compatible with the diagnosis of recent myocardial infarction, as was an electrocardiogram (Fig. 2). Physical examination, on admission, consisted of normal findings, with the exception of a blood pressure of 154/100.

Three days later the patient complained of increased dyspnea. Dullness to percussion and sibilant rales were noted in the lung bases posteriorly. The patient was digitalized; 2.0 cc. of Mercuhydrin was given intramuscularly, and nasal administration of oxygen was started.

No further complication occurred until the 7th day, when hiccuping began, intermittently at first, and then continuously. The rate of hiccuping was every 3 to 6 seconds, and it was of sufficient intensity to shake the bed. The patient was treated with pentobarbital sodium, 0.12 gm. every 4 hours, and 0.4 gm. of quinidine was given intramuscularly every 2 hours for 6 doses, and then every 3 hours for 2 days without relief. On the 10th hospital day, a bilateral phrenic-nerve crush was performed; accessory phrenic nerves, found on both sides, were severed. After the second stage of this procedure the hiccups ceased, although tic-like contractions of the accessory muscles persisted for 3 days, gradually diminishing in intensity and duration. There was no evidence of respiratory embarrassment after this procedure. Fluoroscopy confirmed paralysis of both leaves of the diaphragm. On the 12th hospital day, circulatory collapse occurred, but after 2 injections of 25 mg. of ephedrine sulfate, at 4-hour intervals, the blood pressure and pulse returned to normal. From that time until discharge on March 15, 1952, the clinical course was uneventful. The patient returned to work, and as of June 1, he was working without symptoms.

## Discussion

The cause of hiccups after myocardial infarction is not clearly understood. It has been suggested that infarction of the posterior wall produces irritation of the diaphragmatic pleura, either eliciting a reflex that results in diaphragmatic contraction or causing diaphragmatic contractions by direct stimulation. However, the patient in Case 2 had an anterior infarction. The facts that muscles other than the diaphragm may be involved in singultus, and that both leaves of the diaphragm contract in these cases, are arguments against the theory that direct irritation of the diaphragmatic muscle is the cause. Unilateral singultus has been reported by Elkin,[8] who described a case of abscess of the left trapezius muscle complicated by hiccups involving the left leaf of the diaphragm. His patient responded promptly to left-phrenic-nerve crush. Since the trapezius muscle receives part of its innervation from the second and fourth cervical segments, which contribute to the phrenic nerves, it seems logical that the hiccups were reflex.

Chavany[9] reported a case of coronary-artery disease with angina pectoris accompanied by singultus occurring only on exertion or emotional upset and relieved by rest or nitroglycerin. It does not seem likely that stimulation of the diaphragmatic pleura or irritation of the phrenic nerve would occur in such a case.

Embryologically, the diaphragm is derived from the fourth cervical myotome and because of this, the major portion is innervated by the phrenic nerves (third, fourth and fifth cervical segments). This innervation is mainly on the inferior surface as the nerves pass through the diaphragm before branching. The phrenic nerves carry both afferent and efferent fibers. Branches of the intercostal nerves also innervate the diaphragm and are thought to supply motor fibers only. Sympathetic nerve supply is conveyed from the celiac ganglion through the phrenic plexus, with which the phrenic nerves communicate.

The heart apparently receives its innervation from the superficial and deep cardiac plexuses. These connect with the vagus, the spinal accessory and the cervical sympathetic trunks. Intercommunications between the cervical segments of the spinal cord and sympathetic ganglions, vagus and hypoglossus are known. Therefore, it seems that hiccups in coronary-artery disease are reflex. The efferent nerve is predominantly the phrenic, and its bilateral interruption stops diaphragmatic contraction and singultus.

During the past three years, we have seen 5 cases of singultus complicating myocardial infarction. Of these, the patients in the 2 reported above have lived. One of the 3 who died had multiple embolic phenomena (in the brain, kidneys and spleen); the other 2 received inadequate treatment. Adequate treatment is considered to include relief of gastric dilatation; use of adequate doses of quinidine until hiccups stop or signs of toxicity appear; and, if hiccups persist, fluoroscopic examination to ensure that both diaphragmatic leaves are involved, and in that event, bilateral phrenic-nerve crush. Because of the existence of accessory phrenic nerves in some cases, it is essential to repeat fluoroscopy after this procedure.


## Summary

Two cases of hiccups complicating myocardial infarction treated by bilateral phrenic-nerve crush are reported.

Neither patient experienced any respiratory embarrassment.

Both patients lived and returned to their occupations.


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# DOCTORS AFIELD

## Oliver Goldsmith


Joseph Garland, M.D.

BOSTON


OLIVER Goldsmith's place in literature is undisputed; his authenticity as a physician is more difficult to demonstrate, for his literary achievements stand out against a background of failure in practically everything else that he attempted. Born in 1728 in Ireland, in the hamlet of Lissoy, — possibly the "loveliest village of the plain," —the son of a Protestant clergyman of English descent, he was so shy and unattractive a youth as to be considered more than dull — "a stupid, heavy block-head," according to a contemporary estimate. He was, however, able to enroll in due time at Trinity College, in Dublin, (even if the last of the list) and eventually graduated, still trailing his class. His father died while he was at the University; after his graduation he soon placed on the record an outstanding series of failures: he dissipated his meager inheritance; he was rejected for holy orders, having indulged his life-long passion for bright colors by appearing before the Bishop of Elphin in a scarlet suit; he studied at the law without taking a degree or gaining admission to the bar; and he lost a position as private tutor after a quarrel with his patron.

Having obtained some money from a kindly and credulous uncle he then left Ireland's sod forever, at the age of twenty-four, and made his way to Edinburgh to study medicine. Whatever may have been the extent and the result of this added academic adventure, he remained in the neighborhood of the Scottish University for a year and a half before departing for Leyden, presumably to put the final touches on his medical education. Leyden probably saw little of him, for he shortly set out on his classic tour of the continent, on foot, "with a guinea in his pocket, one shirt on his back, and a flute in his hand." Curiously enough, he probably somewhere did acquire a medical degree on these informal travels, for he was later accepted as a physician in principle at least by Samuel Johnson and Sir Joshua Reynolds, the two persons that he was least likely to have tried to deceive.

Goldsmith next undertook to earn a living at teaching school; failing at this, also, he made apparently his most serious attempt at the practice of medicine by trying for a medical appointment on the Coromandel Coast, on the Bay of Bengal. He was thirty years of age, and whatever his real opinion may have been, he wrote glowingly to his mother of the fortune awaiting an enterprising young physician in India. For some reason undisclosed, although perhaps not too obscure, the plan fell through, and when he then tried at Surgeon's Hall to qualify as a humble hospital mate only, he failed and was rejected. There seemed nothing for him to do, left with the only facility that he had ever demonstrated, but to pick up his pen in earnest, and become a bookseller's hack.

Drudgery that much of this writing was, particularly to a person with Goldsmith's tastes and habits, he had at last found that at which he could qualify and to which he could with some industry apply himself. Uncouth in appearance, unready in speech, with a self-deprecatory sense of humor that many persons still interpreted as stupidity, he found in

literature his true medium of expression. His felicitous style first came to the attention of British readers in his long poem, *The Traveller*, published in 1746, and from that time he came more and more into the affection of the British people. Still his love of splendid clothes, his gambling and his other dissipations, and his inability to hold fast to a guinea continued. His very unthriftiness prevented him from sparing the time necessary to write more of the imaginative works that sprang from his real genius and that he wrote and rewrote until they were nearly perfect in each line and letter.

Goldsmith was a founding member of the celebrated Literary Club, and a favorite of the discerning, if prejudiced, Dr. Johnson. The story is told of the occasion on which Dr. Johnson found him at his lodgings about to be dispossessed for failure to pay his rent, but with a nearly finished novel in the dresser drawer. Glancing through it and finding it of merit, the Great Cham took the manuscript of *The Vicar of Wakefield* to a bookseller and saved the day by obtaining £60 for it. This, however, was but one of many days that had to be saved by one device or another.

Goldsmith's better known works — his two plays, *The Good-natured Man*, produced in 1768, and *She Stoops to Conquer*, first staged in 1773, and *The Deserted Village*, published in 1770 — show the genuine tenderness, the delicacy and the simple humor of his style. These represent the real Goldsmith, in contrast to the oral inarticulateness that called forth the couplet written by Garrick when they had resolved, during an evening at the tavern, each to write the other's epitaph:

> Here lies Nolly Goldsmith, for shortness called Noll,
> Who wrote like an angel, but talked like poor Poll.

The tangible rewards of poetry, however, he found as he described them in *The Deserted Village*:

> Thou source of all my bliss and all my woe,
> That found'st me poor at first and keeps me so;

It was the necessity for more golden guineas to stem the tide of his improvidence that led him, on Reynolds' suggestion, to make one more attempt at practice. In this brief interlude "it is said that he drew out a prescription for a Mrs. Sidebotham which so appalled the apothecary that he refused to make it up; and that, as the lady sided with the apothecary, he threw up the case and his profession at the same time."

At forty-five years of age Goldsmith's health broke down, and although he is alleged to have taken his own case in hand, he was no more successful in following the injunction found in *Luke* 4: 23 than other physicians have been; he had, moreover, neither a good physician nor a good patient. Eventually he sought the advice of other doctors, one of whom finally asked him if his mind was at ease. "No, it is not," he answered, and these were his final words.

Dr. Goldsmith left debts amounting to £2000, and yet Macaulay estimated that in the last seven years of his life he received from his writings £5600, at a time when a pound was worth its weight in silver and a good meal could be had for tenpence.

The world, despite the judgment of the critics, treated him less ill than he treated himself; but, as Johnson counseled, "let not his frailties be remembered: he was a very great man." As a physician he was probably no worse than many of his day who continued in practice.

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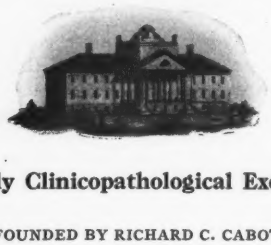
# CASE RECORDS OF THE MASSACHUSETTS GENERAL HOSPITAL



## Weekly Clinicopathological Exercises

FOUNDED BY RICHARD C. CABOT

BENJAMIN CASTLEMAN, M.D., *Editor*

VIRGINIA W. TOWNE, *Assistant Editor*

## CASE 38451

### PRESENTATION OF CASE

A nineteen-year-old boy was admitted to the hospital in coma.

Five hours before admission, just after swimming, the patient suddenly complained of severe pain in the back of the neck; he had not exerted himself greatly or done any diving. Immediately thereafter he fell to the ground, stiffened and began having repetitive clonic movements, described as "shuddering," and incontinence of feces and urine. He was taken to another hospital, where examination showed opisthotonos, bilateral extensor plantar reflexes and bilateral ankle clonus; lumbar puncture showed a few drops of bloody fluid.

Six weeks before entry he first noted severe suboccipital morning headaches accompanied by nausea and vomiting. Examination allegedly showed an elevated blood pressure and blanching of the hands, feet and face; he was treated by bed rest and penicillin. He was advised to undergo further medical investigation, but because he felt somewhat better after one week, he returned to work. The gastrointestinal disturbance subsided, but the headaches persisted and became frontal as well as occipital; insomnia and increasing fatigue developed. One week before admission he had several epistaxes. At no time until the day of admission had there been any disturbance of consciousness, and there was no history of visual disturbances, tinnitus, dyspnea, edema, nocturia or hematuria. There were no known serious illnesses in the past.

Physical examination revealed a well developed, comatose boy, who did not respond to any external stimuli. There was marked opisthotonos. The pupils were 1 to 2 mm. in diameter and equal and did not react to light; examination of the left fundus showed blurring of the upper margin of the disk and hemorrhages. No facial weakness was observed. There was no movement in the limbs in response to painful stimuli. The plantar reflexes were extensor bilaterally; the deep tendon reflexes were difficult to elicit, and the abdominal reflexes were diminished or absent. There was a Grade II, precordial, systolic murmur, with a number of coarse rhonchi and bubbling rales at both lung bases.

The temperature was 104°F., the pulse 100, and the respirations inco-ordinated and slow. The blood pressure was over 300 systolic, 0 diastolic.

Examination of the blood showed a white-cell count of 30,000, with 91 per cent neutrophils and normal red cells and platelets. The urine had a specific gravity of 1.025 and gave a +++ reaction for albumin and an olive sugar reaction; the sediment contained 10 white cells, 6 red cells and many granular and a few hyaline casts per high-power field. Lumbar puncture revealed a grossly bloody spinal fluid under a pressure equivalent to over 600 mm. of water; the fluid contained 1,600,000 red cells per cubic millimeter. Roentgenograms of the skull and cervical vertebras were normal.

The patient remained comatose. A few hours after admission the blood pressure was 180 systolic, 60 diastolic, the temperature 100.4°F., the pulse 100, and the respirations completely irregular at a rate of approximately 1 per minute. A left preretinal hemorrhage, with separation of the retina, was noted. The extensor plantar reflexes could no longer be elicited. Four hours after entry the respirations became more inco-ordinated and finally ceased; ten minutes later the heart stopped beating.

### DIFFERENTIAL DIAGNOSIS

DR. JAMES C. WHITE*: We are confronted with the problem of a nineteen-year-old boy who died of hemorrhage. In discussing this case I want first to make some comments on the record. Since there was no history of a localized head injury with laceration of the brain, presumably the hemorrhage was spontaneous. Spontaneous hemorrhages, if they are due to aneurysm, to tumor or to vascular malformation, do not necessarily occur with exertion; in fact they are almost as likely to occur when a patient is at rest, with the exception of straining at stool and of sexual intercourse.

This patient had an intracranial cerebrospinal-fluid pressure equivalent to 600 mm. of water, which might occur with almost any massive, rapidly expanding intracranial lesion; but the 1,600,000 red cells per cubic millimeter in the spinal fluid would not go with anything but hemorrhage. He had a high blood pressure, which often accompanies an elevated intracranial pressure. The temperature of 104°F. is somewhat high for ordinary intracranial bleeding, but, like the white-cell count of 30,000, with 91 per cent neutrophils, it is compatible with an intracranial hemorrhage. This count is rather low for leukemia, in which a decrease in platelets might account for a bleeding

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tendency. The coarse rales, rhonchi and bubbling in both lung fields were probably due to pulmonary edema, which is a frequent complication of increased intracranial pressure. This patient died with evidence of a pressure cone and with respiratory failure occurring before cardiac failure.

Where did the bleeding come from? Did he have a rupture of an intracranial aneurysm, a vascular malformation, a necrotic tumor that bled or hemorrhage secondary to primary hypertension? Could he have had coarctation of the aorta?

Also, it is interesting to speculate on what made the blurring of the upper margins of the disks and the retinal hemorrhages occur as rapidly as they did. Hamby[1] says that the onset of papilledema is never so rapid; it usually takes a week to produce it; perhaps this was not true papilledema, but diapedesis of red blood cells due to elevated venous pressure. This can account for severe retinitis arising within a few hours of massive intracranial hemorrhage.

The symptoms and signs that this patient had do not localize disease to one hemisphere or the other, but point to a lesion in the midline or brain stem. There were no localizing neurologic signs at all. He rapidly went into coma and had signs of bilateral pyramidal-tract injury, as evidenced by extensor plantar responses. The pupils were equal and small. If he had had a temporal pressure cone, as so many of these patients with massive intracranial hematomas do, I would expect one or the other of the pupils to have been dilated, but the pupils were both small as so often occurs with injuries of the midbrain area with decerebration.

What diagnosis will fit in best with these findings? In view of the decerebrate rigidity, without any localizing cerebral signs, I shall place the lesion in the brain stem somewhere between the hypothalamus and the midbrain. It is interesting that this patient had evidence of a pathologic process going on for six weeks; he had headaches accompanied by nausea and vomiting for that length of time. Magee[2] makes the comment that when a young person without any familial history of migraine has unilateral headaches, an aneurysm is a safe diagnosis. This patient's headaches were bilateral, involving the frontal area as well as the suboccipital. Frontal headache is usually due to stretching of nerves in the falx and tentorium, which run in the ophthalmic division of the trigeminus, and occipital headache to distortion of the upper cervical nerves. He may well have some elevation of intracranial pressure over this period from leakage of blood, which often precedes frank rupture; and it is also possible that hypertension preceded the massive fatal hemorrhage. I am told that he had an elevated blood pressure at the onset of his headaches, but not how much it was elevated. There was a history of blanching of the face, hands and feet; that makes one think of a lesion stimulating the autonomic nuclei in the hypothalamus, such as may occur with tumors in the third ventricle. The unusually high systolic pressure, 300, with a diastolic pressure of 0, I should not expect to occur with any type of malignant hypertension. This peculiar hypertension may have been caused by hypothalamic bleeding although I should not expect it to go so high. It is possible that the blood pressure increased with the increase in the intracranial pressure, since the capillary blood pressure in the brain must be kept above intracranial pressure. Later the blood pressure dropped to 160 systolic, 60 diastolic, which is more consistent with an adjustment to the increase in intracranial pressure. The urine concentrated normally up to 1.025, although he had a +++ test for albumin, for which I cannot account. Sands[3] has reported albuminuria occurring in some patients with massive intracranial bleeding, and Adams and Cohen[4] have noted glycosuria. I do not believe this patient had a pheochromocytoma, for patients with epinephrine-secreting tumors rarely get into difficulties during their first hypertensive episodes. Furthermore, with a systolic blood pressure of 300 and a diastolic of 0, I do not think he had primary malignant hypertension and secondary rupture of an intracranial vessel. Of course, I should like to have the information that tests made during a routine hypertensive work-up could give us. It is often difficult to differentiate malignant hypertension from brain tumor. In 1948 Palmer, Nyssens and I[5] wrote about the difficulties in the differential diagnosis of these two conditions.

What other lesions in the brain stem will produce massive bleeding? Hypothalamic tumors can cause profound changes in the blood pressure, with cardiac manifestations, episodes of sweating and blanching in the hands and feet. Penfield[6] described such a case in 1929, and others have been reported by Urechia.[7] By electric stimulation of the lateral walls of the third ventricle in the course of operations on hydrocephalic patients I have produced striking elevations of the blood pressure and pulse rate, so that a lesion in this region can cause many of these disturbances.

Sometimes, a glioma in the island of Reil will rupture and bleed into the ventricles, causing nuchal rigidity with a massive blood clot. Sands[3] reported the case of a patient who had an angioma of the vermis of the cerebellum who behaved very much as this patient did, so that is a further possibility to consider. Such lesions, however, should produce localizing signs.

All things considered, this boy's death may be best accounted for by the rupture of a vessel at the base of the brain, with blood entering the ventricles through the hypothalamus or upper midbrain. My diagnosis, therefore, is massive subarachnoid and intraventricular hemorrhage. This bleed-

ing may have come either from a vascular tumor of the hypothalamus or brain stem or from a ruptured congenital aneurysm. In addition, he had a cerebellar pressure cone and pulmonary edema. There is no evidence of a temporal pressure cone, but that does not mean that he did not have one. If he did, he may also have had secondary hemorrhage in the midbrain.

DR. MANUCHER JAVID: The history, as it has been presented here, was not available when this patient was brought to the hospital. The only information that we had was that there was a question of a head injury after swimming.

Examination revealed the abnormal findings that have been described. It was our impression that

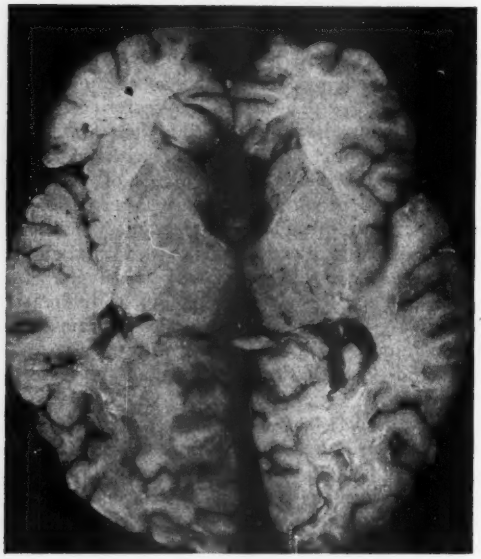

FIGURE 1.

we were dealing with massive intracranial bleeding due to a ruptured intracranial aneurysm. X-ray films of the cervical spine and skull were taken to rule out additional injuries. By this time, we were able to obtain some information about the patient from the family, who gave a history of suboccipital headaches, accompanied by nausea and vomiting, for at least six weeks, and of a high blood pressure when he was examined six weeks before entry. We believed that he had malignant hypertension as well as subarachnoid hemorrhage due to ruptured aneurysm. Since he was in a terminal stage and was a poor candidate for carotid arteriography, we saw no point in subjecting him to this procedure. One more point: the patient did have dilated pupils, which have not been mentioned, so that he probably had temporal pressure cones prior to death.

### CLINICAL DIAGNOSES

Subarachnoid hemorrhage, due to ruptured intracranial aneurysm.
Malignant hypertension.

### DR. WHITE'S DIAGNOSIS

Massive subarachnoid and intraventricular hemorrhage.
?Bleeding vascular tumor.
?Ruptured congenital aneurysm.

### ANATOMICAL DIAGNOSES

*Ruptured congenital aneurysm, circle of Willis.*
*Massive subarachnoid, intraventricular and intracerebral hemorrhage.*
Pulmonary congestion and edema.

### PATHOLOGICAL DISCUSSION

DR. ROBERT H. FENNELL, JR.: The heart was of normal size, and the lungs were severely congested and edematous. We attributed the pulmonary edema and congestion to the changes within the intracranial cavity and the hypertension that the patient had was also probably due to this. Certainly, hypertension of the severity indicated had not been present very long with a heart of normal size. The kidneys showed no changes to suggest malignant nephrosclerosis or any other renal disease.

Dr. Richardson will describe the neuropathologic findings.

DR. EDWARD P. RICHARDSON, JR.: This illustration (Fig. 1) of a horizontal section of the brain shows a large amount of blood within the ventricular system, and even more striking the fact that the anterior portion of the corpus callosum and the entire septum pellucidum are torn apart and destroyed by the hemorrhage. The source of the bleeding was a ruptured saccular aneurysm, which was situated at the junction of the left anterior cerebral and anterior communicating arteries. The location of the aneurysm was very nearly in the midline. At its rupture, the hemorrhage had extended upward, producing the intraventricular hemorrhage and the destruction of midline structures already mentioned. There was also a small amount of hemorrhage that had extended laterally into the inferior aspect of the left frontal lobe, producing further intracerebral hemorrhage. The subarachnoid space at the base of the brain and over the anterior surfaces of the brain stem and cerebellum was completely filled with blood. The cerebral aqueduct was dilated because of the large amount of blood that had entered it from the ventricles above. There was little, if any, cerebellar or temporal pressure coning. However, the entire brain stem was encased in a large mass of subarachnoid blood.

The aneurysm was of the type generally considered to be the result of a congenital defect in the

wall of the vessel, characteristically occurring at an arterial bifurcation. The hemorrhage and associated destruction of brain tissue appeared very recent, and were unquestionably the cause of the patient's acute and severe illness and death.

The history of headaches during the six weeks before death is not clearly explained by the findings at autopsy. Our experience with other cases indicates that leakage of blood may occur from aneurysms before a major rupture takes place, and that this leakage is attended by such premonitory symptoms as occurred here. In this case, we have no clear pathological evidence of previous subarachnoid bleedings, but it could well have been covered up by the final extensive hemorrhage.

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## CASE 38452

### Presentation of Case

A twenty-three-year-old para III, gravida III, was admitted to the hospital because of right lower abdominal pain.

About nineteen months prior to entry the patient experienced for the first time a sharp, stabbing pain in the right lower quadrant that lasted twelve hours and was relieved by codeine. Since that time bouts of similar pain had occurred approximately every two or three months. On the morning of admission she noted the sudden onset of pain in the right lower quadrant described as a constant, deep ache with radiation into the right flank and down the right leg, which was not relieved by 3 codeine tablets. She vomited twice.

The patient had felt well until the beginning of the pain. She had had three full-term normal deliveries five, three and one-half, and two and one-half years before entry. Since the birth of her first child she had had a whitish vaginal discharge, which she thought had increased somewhat recently. She denied venereal infection. The menarche had occurred at thirteen years of age, and menses had occurred every twenty-eight to thirty days, lasting five days with a normal flow. Her last menstrual period ended seven days before admission to the hospital. There were no bowel or urinary-tract symptoms. She had been married six years but was separated from her husband from time to time because of his excessive drinking.

Physical examination showed a well developed woman in no acute distress. The heart and lungs were normal. Both lower quadrants were tender, the right much more so than the left. There was slight rebound tenderness and no real spasm except on deep palpation. Peristalsis was normal, and there was a positive psoas sign on the right. On pelvic examination there was considerable whitish mucoid discharge in the vagina. There was exquisite tenderness on motion of the cervix, mainly on the right. The uterus was enlarged to about twice the normal size and was firm. There was severe tenderness in the right vault, and a firm, tender, rounded mass measuring 3 to 4 cm. in diameter. The left vault was slightly tender but free of masses. Rectal examination disclosed nothing further.

The temperature was 100°F., the pulse 95, and the respirations 24. The blood pressure was 120 systolic, 70 diastolic.

The urine gave a + test for sugar; the sediment contained occasional white cells and red cells. Examination of the blood revealed a hemoglobin of 11 gm., and a white-cell count of 12,000, with 90 per cent neutrophils.

On the second hospital day examination revealed marked tenderness and spasm in the right lower quadrant but very little tenderness on motion of the cervix or in the right vault. During the next three days the pain varied in severity, and at times the patient felt anorexic but did not vomit. The right-sided mass continued to be tender but did not increase in size. The temperature and white-cell count remained slightly elevated despite the administration of 600,000 units of penicillin started on the third hospital day.

On the fifth hospital day an operation was performed.

### Differential Diagnosis

Dr. Howard Ulfelder*: This young married woman of known fertility and good health came into the hospital with an acute illness of less than a day's duration. The illness was characterized by sudden, right-lower-quadrant, constant, unremitting, aching, deep pain, which was followed by vomiting. Whether the codeine taken to relieve the pain was responsible for the vomiting I do not know; nausea was not mentioned. This pain apparently radiated to the right flank and down the right leg, and examination in the hospital disclosed tenderness in the right lower quadrant. Spasm may or may not have been present; it was not an outstanding feature of the examination. The intestinal tract showed normal peristalsis. She had a positive psoas sign, which I assume to mean that when she was asked to try to flex her hip against a certain amount of resistance she had pain in the right lower quadrant. Other findings at the time of admission are the enlarged uterus, described as twice the normal size,

*Assistant surgeon, Massachusetts General Hospital.

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with marked tenderness to the right of the uterus in the vault, and a space-filling, tender object 3 or 4 cm. in diameter. She had slight fever and moderate elevation in the white-cell count, with a definite increase in the percentage of neutrophils. She had some cells in the urinary sediment, both red and white, but not in great amount. The hemoglobin was a little lower than one would expect in a healthy young woman but not enough so to suggest an acute massive hemorrhage as the cause of admission.

The differential diagnoses in a situation of this sort, I should think, include infection, interference with blood supply to some organ in this area, hemorrhage into an organ and obstruction to some smooth-muscle viscus. The localizing findings in this patient point to the right iliac fossa and the true pelvis. The radiation of the pain to the flank and down the leg, the positive psoas sign and the tenderness on abdominal pressure point to the right iliac fossa; however, the tender mass was in the true pelvis, which is not the right iliac fossa — although they are adjacent.

There are structures in the right iliac fossa — the right ureter and the cecum — that can be examined by the roentgenologist. I suspect that there were no abdominal or pelvic x-ray films, but I hope there were either pyelograms or a barium-enema examination.

DR. BENJAMIN CASTLEMAN: No x-ray films at all were taken.

DR. ULFELDER: In that case I cannot exclude a lesion in that area on the basis of the x-ray findings as I had hoped.

Other leads that I must explore include the history of previous attacks of pain in the same location that lasted approximately twelve hours — apparently she had at least four (enough to be significant), occurring without known provocation and so far as I can tell subsiding spontaneously. The history makes pregnancy unlikely. She had a normal menstrual history, she was known to have been fertile previously, and she had a period that was not described as having been abnormal in any way and ended seven days before admission. I assume that this pain started about midcycle for this patient. Whether this means that ovulation played any part in this picture I am not yet prepared to say. Endometriosis I should consider unlikely on the basis of the history. She did not have the characteristic dysmenorrhea, and she had had three pregnancies, all within the previous five years.

Her course in the hospital is the next aid in arriving at a diagnosis. I assume, from the description that the diagnosis at the time of admission was deferred, that she was not considered to be desperately ill and that a program of supportive therapy was therefore instituted in the hope that a definite diagnosis could be arrived at under observation. One assumes from the history that on the supportive therapy she neither grew worse nor improved. One important feature of this early period of observation is confirmation of the finding of the mass in the pelvis. I am sure that when she first came in she was much too tender for any examiner to be absolutely certain that a mass was present. Over the course of the next few days the tenderness became somewhat less pronounced, and the presence of the mass was confirmed. One gathers that chemotherapy made little difference, and, therefore, after a short period during which it was hoped that chemotherapy would bring about some dramatic improvement, the surgeons decided to operate on her.

Whether at the time of exploration a more definite diagnosis had been made, I cannot tell from the record. No studies made while the patient was in the hospital under observation are of any particular help to me. There are some significant omissions from the protocol if they are really omissions. In the first place, a fasting blood sugar was not reported. That means to me that the physicians were not particularly impressed with the finding in the urine. Again, a Gram stain on the secretion from the vagina and cervix was not reported. The question of an acute pyosalpingitis of gonococcal origin would have prompted most physicians to make that Gram stain although it is not particularly significant unless it is positive. Thirdly, an Aschheim-Zondek test was not reported. The persistent presence of a mass in the right vault and the notation that the uterus was twice the normal size at the time of admission, regardless of the menstrual history should have prompted an Aschheim-Zondek test. The lack of x-ray films I consider a significant omission also.

DR. CASTLEMAN: A culture of the vaginal discharge showed abundant growth of *Staphylococcus aureus* and was negative for gonococcus. An Aschheim-Zondek test was negative.

DR. ULFELDER: What is the differential diagnosis in this patient? First of all, she could have had an acute suppurative salpingitis, so-called pelvic inflammatory disease, which would explain the picture about as well as any other single lesion. However, an acute appendicitis, with abscess, the appendix lying over the brim and partly in the true pelvis, could also explain it. A third possibility is an acute accident to the right ovary or to a cystic right ovary. This acute accident could have been thrombosis or hemorrhage into the cyst. Somewhat less likely conditions — because they do not explain all the findings — include a lesion of the right ureter, particularly a calculus, which could have caused a good many of the symptoms but would not explain the pelvic findings, or a lesion of the small bowel. This history is not unusual in patients with intussusception that does not completely obstruct. A Meckel diverticulum or some other lesion of the small bowel that produced intussusception could cause abdominal pain in the period before a small-bowel obstruction developed. There may be quite

a long interval from the time intussusception begins in the small bowel to the complete occlusion of the involved loop.

My problem is whether to try to make one lesion explain the entire picture or whether to assume that the mass felt in the right vault was more or less an incidental finding but so adjacent to the primary lesion that it appeared to be tender — appeared to be the chief difficulty. Needless to say, I have not arrived at a diagnosis in my own mind. I had hoped that the x-ray films would exclude some of the possibilities for me, although I did not expect that they would actually make the diagnosis.

I have excluded endometriosis and tubal pregnancy by history. I have excluded a ureteral calculus, which would not explain the mass. I have not excluded an acute appendicitis although the history of onset and the course in the hospital are not consistent, but if there is one thing that is consistent about acute appendicitis it is its inconsistency as far as its behavior is concerned. I do not believe it was torsion of a right ovary, for then I should expect the mass to have become more tender and to have increased in size during the period of observation in the hospital. I am left, therefore, with the possibility of an acute appendicitis with abscess, which I shall put lowest on my list, the possibility of some lesion of the small bowel and finally, what I consider the most likely diagnosis, an acute suppurative salpingitis — that is, pelvic inflammatory disease.

Dr. Walter Bauer: What do you think of hemorrhage into a cyst?

Dr. Ulfelder: I should expect that such a mass would get larger and more tender during the time of observation. Patients with such vascular accidents usually have a much higher white-cell count and less fever at the time of onset.

Dr. John T. Quinby: Do you think the diagnosis of acute salpingitis is consistent with the history of episodes of right-lower-quadrant pain in the past?

Dr. Ulfelder: I think pelvic inflammatory disease, diverticulum, a cyst of the right ovary that twisted and untwisted or almost any of the diagnoses that I have raised could have caused the previous episodes; therefore, I have not let it influence me one way or the other.

Dr. Castleman: Under anesthesia, the surgeon examined the patient before operation and felt a large cyst, which lay in the midline, was movable and measured about 12 by 10 cm., and higher in the right vault, another harder mass, which measured about 5 cm. in diameter. Do you wish to comment about that?

Dr. Ulfelder: That the patient was under anesthesia does not make the examination more accurate than the initial examination. The examiner may be badly fooled even when the patient is well relaxed. It does not help me to make a more accurate diagnosis from the list of my differential diagnoses. I assume that the larger cystic mass was what was previously called the two-times-enlarged uterus and the other was the tender mass found during the patient's preoperative course.

### Clinical Diagnoses

Right tubal abscess.
?Twisted cyst with tubal abscess.
Twisted ovarian cyst (after ether examination).

### Dr. Ulfelder's Diagnosis

Acute suppurative salpingitis.

### Anatomical Diagnoses

*Paraovarian cyst, with twisted pedicle.*
Infarcted right ovary.

### Pathological Discussion

Dr. Castleman: At operation, the large midline mass proved to be a hemorrhagic paraovarian cyst, which had twisted about 360° counterclockwise and had also twisted the right ovary along with it. The small hard mass was the infarcted right ovary secondary to the twist of the large paraovarian cyst. The tube itself had some hemorrhage into it, but there was no evidence of previous infection. The whole mass was removed en bloc. I suppose there had been some twisting and untwisting over the past nineteen months.

A Physician: How large was the paraovarian cyst?

Dr. Castleman: Twelve by 8 by 8 cm; it was good sized, which is not at all uncommon. Often, a large noninfarcted paraovarian cyst is removed with a preoperative diagnosis of ovarian cyst, and a normal ovary is found beside it.

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## CHOICE OF THERAPY FOR PNEUMONIA

THERE have been a number of reports of studies designed primarily to evaluate the relative effectiveness of the antibiotics now available in the treatment of pneumonia. In Great Britain, and presumably in most countries other than the United States, the problem of the choice of a therapeutic agent is complicated and often dominated by considerations of cost. Many varieties of pneumonia respond as well to sulfonamides or penicillin as they do to the so-called broad-spectrum antibiotics — aureomycin, terramycin and chloramphenicol (Chloromycetin).

The production of each of these antibiotics is controlled by patent rights assigned to individual manufacturers; this enables the fixing of prices without necessarily any relation to cost, whereas the production of penicillin, which was developed largely with the aid of Government-subsidized research (mainly in Great Britain and the United States) during World War II, has become highly competitive. With no exclusive patent rights, penicillin can be produced in Great Britain (and other countries as well) and at a much lower cost, in spite of the fact that comparable methods of production are used.

Even the cost of chloramphenicol, which is produced for the most part synthetically, and presumably at appreciably less expense, has been maintained at essentially the same monopoly level as that of aureomycin and terramycin, which are produced by fermentation procedures exclusively. The sulfonamide drugs, because of the relative simplicity of their chemical production in bulk and because of the level of competition, have likewise sold at a small fraction of the cost of the broad-spectrum antibiotics.

Since the patents on the broad-spectrum antibiotics are held largely by American companies and since large-scale use would mean the export of dollars, which the British need for other purposes, the Medical Research Council of Great Britain set out in 1950 to determine whether there was indeed any great advantage in using expensive American-controlled products in preference to sulfonamides or penicillin made in Great Britain under local patents or without patent restrictions. The results of an investigation of this problem are contained in a report by a subcommittee of the Antibiotic Clinical Trials (Nontuberculous) Committee of the Medical Research Council.[1]

The therapeutic trials were carried out in four centers — two in London, one in Sheffield, and one in Glasgow. Cases diagnosed as pneumonia on admission were allotted at random to one of three treatment groups: the first was given aureomycin, the second chloramphenicol, and the third "standard treatment," most of the patients in the last group receiving penicillin and a few sulfonamides. In all, 267 cases were studied; the various groups were found to be comparable in every respect, and the results of treatment were similar in each group. It was concluded that penicillin was at least as

valuable as the other two antibiotics, and symptoms of drug toxicity were much less frequent with penicillin than with aureomycin or chloramphenicol.

Treatment with aureomycin was found to be more than ten times as expensive as penicillin therapy, and treatment with chloramphenicol more than nine times as expensive as that of penicillin. It was therefore concluded that in a choice among aureomycin, chloramphenicol and penicillin, the last given by injections is the best treatment for clinical pneumonia. The possible value of sulfonamides was not taken into account because they were not used in enough cases for comparison with the other drugs in this particular trial.

A separate report by one of the group of collaborating investigators from Glasgow accompanied the Medical Research Council's report. In the Glasgow report,[2] 79 patients suffering from pneumonia were included in a comparative trial of aureomycin and penicillin, both given by mouth; the two groups of cases were quite comparable in every respect when the treatment was begun. The results of the study suggested that aureomycin was no more effective than penicillin for the average case. In extremely severe cases with systemic complications, it was concluded that early treatment, preferably by injection, is necessary for the most favorable results; 4 of the 5 deaths in this study occurred in patients in whom cardiovascular complications were present.

Although these studies were sponsored by the Medical Research Council of Great Britain, the number of cases was quite small and probably inadequate. There have been other attempts to compare the results of various forms of treatment of bacterial pneumonias in the United States. These, likewise, have been based upon comparisons of relatively small numbers of cases. As was to be expected, between two thirds and three quarters of these cases were caused by the pneumococcus in each of the studies. In a large general hospital in Philadelphia,[3] such a study carried out in 93 cases indicated that aureomycin, chloramphenicol and penicillin by mouth, or penicillin by injection, all gave results that, at least from the point of view of the end results, were indistinguishable. The response of the patients in this group, as measured by the rapidity with which the temperature returned to normal, seemed more rapid when penicillin was used. In another large hospital in Seattle, Washington, 50 patients were treated with aureomycin, and 50 with chloramphenicol.[4] Both groups responded favorably, and no superiority could be claimed for one antibiotic over the other. In this series 81 of the 100 patients were treated with 1 gm. in a single dose each day. The results in these cases seemed to be, in general, excellent. There were only a few cases in which larger doses were considered necessary.

In the British study,[1] the average dose was 26 gm. of aureomycin and 23 gm. of chloramphenicol per patient. This is about five times the amount used in the Seattle study,[4] and yet it was believed that the smaller dose was adequate for the great majority of cases. A study designed specifically to determine whether a small dose of aureomycin was effective was carried out in Memphis, Tennessee,[5] where 70 patients with acute nontuberculous bacterial pneumonia were treated with 1 gm. of aureomycin daily administered orally in four divided doses. The cases varied in severity, and some were considered to be extremely severe. There were no deaths, and the results suggested that the therapeutic regimen used, which averaged a total of only 5 gm. per patient, was adequate in most cases and seemed well adapted for the home treatment of the average case of acute bacterial pneumonia. These studies answer, in part, the objection raised by the British workers to the high cost.

The only toxic effect observed from the small doses used in this study consisted of a mild diarrhea (three or four semiliquid stools a day for three days) in 1 patient. In the Philadelphia study there was a low incidence of toxicity although in several patients diarrhea proved troublesome but did not require discontinuance of the treatment. The average dose of aureomycin used by the Philadelphia group was 8 gm.

The value of all these studies, however, is minimized by the fact that only small numbers of cases were employed. Since penicillin, the broad-spectrum antibiotics and the sulfonamide drugs are all highly effective in pneumococcal pneumonias and since the pneumococcus causes the bulk of cases, especially those in the hospitals where these studies were carried out, the results of these studies of the

treatment of pneumococcal pneumonias cannot be considered as entirely conclusive. A much more extensive experience, with a sufficient number of cases of nonpneumococcal pneumonia, particularly of the varieties that are known not to be favorably influenced by penicillin and the sulfonamides, would be necessary to bring out the true advantages of the broad-spectrum antibiotics. In individual cases, therefore, physicians should still be on the alert for such cases and should use aureomycin or terramycin for the optimum effect. Because of the recent reports on the occurrence of many cases of fatal aplastic anemia from chloramphenicol, that drug should be avoided unless the other antibiotics fail or cannot be tolerated, the disease is severe and the patient is progressing poorly. In the great majority of cases, however, the results of these studies indicate quite clearly that the less expensive and simpler drugs, penicillin and sulfonamides, are entirely adequate.

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## PASTOR AND PHYSICIAN

The little *Journal of Pastoral Care*, now in its fifth volume, is doing much to explain to the pastor the functions of the physician, and to the physician those of the pastor, and to bridge the gaps that admittedly still exist between the caring for men's minds and bodies and the care of their bodies and souls.

To be concerned about the spiritual welfare of his flock has always been one of the first obligations of the good pastor. In sickness and in health the kindly, understanding, guiding word and counsel have been fruits of his dedication.

On the other hand, in the past forty years or more, the branch of medicine known as psychiatry has been paying increasing attention to the kind of human disability that is characterized by partially incapacitating symptoms, which apparently do not originate in clear-cut physical disease. Such disabilities are usually considered "emotional disorders." Since emotional reactions seem dependent upon and to arise from the attitudes, points of view, personality traits and even character of the individual person, the clergy would be exhibiting a grasp of the relevant, at least, in being interested in what psychiatry might have to say, and possibly to teach, about illness of a part or of the whole personality. In its conception the malfunctioning personality could be suffering with "soul sickness." Furthermore, the clergy's interest would not necessarily have complete initiation from introspection. Psychiatrists, except for exponents who preferred to think they were working in an exact science, wondered if the church might be able to help with some of their problems. For example, Jung had said, "Among all my patients in the second half of life — that is to say, over thirty-five — there has not been one whose problem in the last resort was not that of finding a religious outlook on life."

It could be explained that the clergy, in its approach to the findings of psychiatry, was not, of course, thereby in any degree revealing a defect in or relinquishing of its faith. Just as advances in medical and surgical treatment could not today be rejected as unholy, so the technical means that might offer profounder perception into and treatment for personality deviations might be included in the Christian armament for fighting the devil.

In the last quarter century the clergy has, in fact, become more and more engaged in counseling along psychotherapeutic principles. Seminars, conferences and individual and group teaching have brought religion and psychiatry into closer association and common appreciation. Differences in opinion must have arisen, especially on the fundamental one, the definition and conception of God. Men whose primary interest is scientifically inclined do not have a uniform religious belief, and generally they do not accept as proved fact a theological interpretation of the essence of the Deity. Most men of science, however, if their intellectual vision is not obscured or contracted by ideational blinders, will not quarrel with a faith that makes for greater understanding.

Unfortunately, a professed and even sincere Christian religious belief does not prevent the professor from doing harm in the world. If the man who earnestly thinks and says, "I believe in God," were thereby arrested from wrongdoing, man's inhumanity to man would have, long since, lessened to an obvious and optimistically encouraging extent. It might be hypothesized, with humility, that God is more interested in men's being and doing good than He is in polling their votes on His reality in specific terms.

It is known, of course, that the clergy is not always quite content in accepting good works as comparable with the recognition and acceptance of God. There is, however, no charm in the stating of a phrase, no matter how honestly or frequently it may be reiterated. The avowal, to be sufficiently effective, has to be pervasive throughout the whole of the individual's actions. Also, there is really no proof that people who are not quite sure just what they think and feel about God do more harm than those who think they hold, or who do actually and consistently hold, a definite conviction on the reality of a Supreme Being.

Nevertheless, the category of definitions should not hinder the church and psychiatry from working together productively. If the psychiatrist, on his part, can comprehend that man may never be self-sufficient and if he sees that his branch of knowledge gives him no authoritative, decisive insight or foresight into man's future, he may benefit in learning, if he does not already know it, that faith can have therapeutic value. If the pastor, on his part, will continue to be forebearing and will admit that good will and good works may be akin to godliness, and if he keeps in mind that all current psychiatric theories are not necessarily divine revelation through scientific channels, he may learn or be reinforced in his knowledge that all emotional suffering and illness are not due to imperfect faith. He may also learn that all emotional illness does not respond to counseling and is not cured by discussion or catharsis, and he should become appreciative of when not to push these elements too far.

So many considerations are present in the question of what makes a good therapist, cleric or psychiatrist that it is disputable whether or not academic training alone gives satisfactory results. Humility, knowledge, goodness and understanding should, perhaps, be enough. Yet it is not always so. Factors such as worldly values sometimes have potent therapeutic force, and patients may react favorably to what seems to them to be an answer to their conscious needs, whether spiritual or material.

In their separate and combined therapies, psychiatry and the church might weigh the possibility that today, and throughout whatever part of eternity may have been made manifest thus far, man's first and most powerful enemy is not sex but his own egotism, his own individualistic self-interest, not yet enlightened enough to guarantee his survival on the earth.

## NURSING FELLOWSHIP FUND

CREATED only last summer at the Biennial Nursing Convention in Atlantic City, the Nursing Fellowship Fund is designed "by and for nurse educators to provide the opportunity for advanced education to qualified nurses who would otherwise not be able to avail themselves of such an educational experience." As many $2,000 fellowships as can be obtained will provide opportunities for a year's study at the Division of Nursing Education of Teachers College, Columbia University. Some of the courses of study will be of college grade; more, it is anticipated, will be directed toward the master's degree, whereas a few will be awarded to candidates for a Ph.D.

Beginning last September 18,000 graduate nurses in the field of nursing education were asked to contribute to the fund — the first time that nurses have developed their own national fund-raising organization for the advancement of their own professional training. Vice-chairman of the Fund is Miss Ruth Sleeper, director of nurses at the Massachusetts General Hospital and president of the National League of Nursing.

The various nursing associations that had existed prior to the present decade instituted, in 1950, a voluntary study of their own overlapping aims and activities that resulted in two national organizations.* The American Nurses Association continued

*Editorial. Nursing reorganizes. *New Eng. J. Med.* 246:878, 1952.

in existence with its objects defined as promoting the professional, general and economic welfare of nurses. The new National League for Nursing was established to foster the development and improvement of organized nursing services and education for nursing. The Nursing Fellowship Fund, participation in which will be a source of pride to any nurse, is based on the sound principle that those who teach should be given the opportunity for their own continuance in higher education.

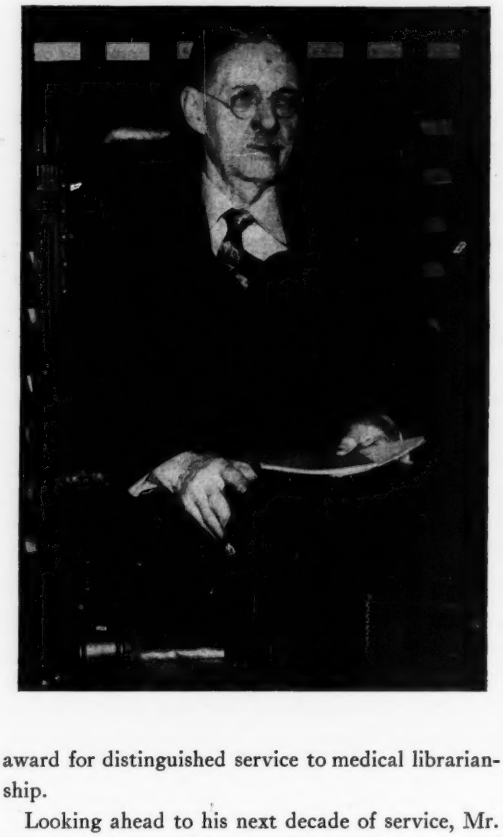
## *EX LIBRIS*: JAMES F. BALLARD

THOSE interested in medical literature the world over may turn their attention for a moment this fall to the contemplation of a unique if relatively unheralded event. This was the quiet observance, on October 24, of the sixtieth anniversary of the association between the Boston Medical Library and its present director, James F. Ballard.

On October 24, 1892, this distinguished librarian, then a lad of fourteen, and, he avers, distinctly undistinguished, secured a job as messenger at the library, at $3 a week, for a trial period only. On that day an association began that eventually made James Ballard and the library synonymous in the minds of those who turn their minds to libraries at all.

During an early stage in this career, in 1900, Mr. Ballard watched tenderly over the construction of the present library building at the edge of the fields and swamps that made up the Boston Fens. Since then, turning to more distant horizons, he has made an extensive trip through Europe in the interests of the China Board of the Rockefeller Foundation to purchase a medical library for the Peiping Union College. He has conducted library surveys for Louisville, Detroit and Worcester. In 1928 he assembled a medical library for the Rochester University Medical School. Meanwhile, on the home grounds, he has made the largest collection of medical incunabula in the hemisphere.

As if these activities were not enough, young Mr. Ballard is now a member of the board of trustees of the Milton Public Library, consulting librarian to the Boston City Hospital, Boston University School of Medicine, Tufts College Medical School and the Armed Forces Medical Library in Washington, and book-review editor of the *Journal*. He has served as chairman of the board of trustees of the Massachusetts State Library and has been president of the International Medical Library Association. In 1951 he received the Marcia C. Noyes



award for distinguished service to medical librarianship.

Looking ahead to his next decade of service, Mr. Ballard is currently immersed in the plans for further enlarging and modernizing his library — now the third largest of its kind in the country.

*Moral fitness and intellectual training are not taken into account in these days of medical disquietude, and consequently society at large is blameable for some of the disadvantages and evils of quackery.*

Boston M. & S. J., *November 10, 1852*

## BY THE LONDON POST

### AN ENGLISH COUNTRY PRACTICE

AUGUST being the traditional holiday month in England, I was recently spending a few days in a small town on our South West Coast. My host was driving me in his car one evening and pointed out

a new building, which, he explained, was his doctor's surgery (English for a doctor's office). When I said I was interested to know how a country practice was working under present conditions, my host suggested I call up the doctor and ask him to show me around. The result was a cordial invitation to visit him next evening, when he described with enthusiasm and in great detail how he and his partner had organized their practice. He told me that his original partner had died shortly after the start of the National Health Service in 1948, leaving his records in chaos, and that this had made him decide to break with the British custom of conducting one's practice from one's house and to build a central surgery, where two partners could see their patients and where a satisfactory record system could be established. The modern ranch type of building, which my host had pointed out, was the result of this idea. Accommodation is provided for two doctors and a dentist. There is no one resident on the premises, but an ingenious arrangement enables patients to get hold of a doctor at any time of the day or night. In the entrance lobby, which is always open, there is a telephone, connected to the home of the doctor on duty whenever the building is left unattended. Above the telephone an instruction reads "If you wish to speak to the doctor, lift the 'phone, turn the handle briskly and wait for an answer." There is a seat beside the phone so that anyone may wait in comfort until the doctor arrives.

The first door inside the building opens into a well equipped casualty room, with a small operating table and double doors wide enough to take a stretcher. Next comes the patient's waiting room, with modern furnishings and thermostatically controlled electric tubular heating — a rare luxury even in English homes! Opposite the waiting room is the secretary's office, which is situated between the consulting rooms of the two partners and has a door opening into each. The consulting rooms are well furnished, and each has a curtained cubicle for the examination of patients. Hot water is supplied from a thermostatically controlled heater. Patients for the dentist ring a special bell and are admitted by his receptionist, and patients for the doctor call at the secretary's office and wait in the waiting room until summoned. Meanwhile their record cards are removed from the filing cabinet and placed in their correct order on the doctor's desk.

The doctor assured me that the relation between the physician and the dentist was most satisfactory, the dentist finding it convenient to have an anesthetist at hand and the dental x-ray apparatus often being useful for minor accidents. I said that I thought that by practicing from such well equipped and well organized premises the doctor-patient relation must also be good. To my surprise my friend shook his head and said that he was afraid the patients either thought the doctors must be doing very well to be able to afford to build such a place or assumed that it must be part of the National Health Service and took it all for granted! In point of fact, the cost of the building was paid almost entirely by the practice itself — only a small allowance being granted by the N. H. S., the reward for the doctors concerned not being monetary but the satisfaction of being able to treat their patients with efficiency and in congenial surroundings. From this my friend assured me that he was able to find a renewed interest in his work and a fresh enthusiasm for general practice, which he believes to be the most enjoyable, if one of the most exacting, branches of medicine. Furthermore, he has derived great peace of mind from the knowledge that his practice could be taken over in running order with complete records at any time by another doctor.

There are few practices like this I am sure, but here is an example of free enterprise working within the N. H. S., and if general practice is to remain the backbone of the medical profession in this or any other country, the more efforts like this, the better.

## The Hunterian Method

Doctors have long been known for being great collectors, and the temporary return to London of part of Dr. William Hunter's collection of pictures is a reminder of his amazing industry and that of his younger brother John.

Born into a large family in Scotland (William in 1718 and John in 1729) they both migrated to the Anatomy School at St. George's Hospital in London, where they both made their fame as anatomists, William later becoming an obstetrician and John a surgeon. They had interests so wide, however, that Lord Moynihan said of John that there had probably never been a man in one profession with so wide an intellectual interest and so profound a knowledge of so many varied subjects wholly derived from direct personal inquiry and observation.

It was the search for knowledge that stimulated both brothers to start collecting. The Hunterian Museum of the Royal College of Surgeons is the collection of specimens prepared by John, and at the time of his death in 1793 these numbered 8000. To cover the enormous amount of work he planned for each day, he is said to have started work at 6 a.m., and continuing until 1 or 2 o'clock the next morning, with only a break for dinner and an hour's sleep at 4 p.m. He is said to have dissected at least 500 species of animals, and he had a farm where he conducted experiments. In addition, his surgical opinion was widely sought.

William started collecting at an early age. His first specimens were medical, their nature being determined by the use he could make of them in teaching and research. As his interests widened he

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added specimens of mammals, reptiles, birds, rocks and fossils. These were followed by a large number of books, manuscripts, coins, prints and pictures acquired during the later years of his life.

Although in this day of specialization, both brothers would be criticized for being too diffuse in their outlook, there is surely much to be learned from their lives. They were, of course, typical of the efficient, self-confident Scots, who have been so successful not only in migrating from Scotland to England but also to the farthest corners of the earth. Nevertheless, the hard work and industry that these men showed, and above all the way in which they applied the simple method of inquiry into scientific problems, should be reflected on in these days of complicated research.

### The Cost of Social Security

The third annual report of the Ministry of National Insurance, published this month, calls further attention to the vast cost to the nation of the social-security schemes. The rapid increase in the number of persons of pensionable age to a total of 4,100,000 is one of the major financial burdens on the scheme, and the report estimates that in 1953–54 the retirement pensions will cost nearly £350,000,000. At the end of 1951 about 3,100,000 families containing nearly 8,000,000 children were receiving family allowances of 5s. a week for each child after the first. Statistics show, however, that the average size of the family is contracting, and that about 65 per cent in receipt of allowances only contained 2 children.

The Industrial Injuries Scheme cost over £8,750,000 in the year, most of the claims coming from the heavy industries and coal mining accounting for more than a third of the claims.

Owing to the severe epidemic of virus A influenza that swept the country in January, 1951, the number of persons receiving sickness benefit that month was the highest recorded since the scheme started in 1948, 1,500,000 persons being in receipt of benefit. The Ministry of Health followed the epidemic by a careful study of the numbers of new sickness claims at local offices of the Ministry of National Insurance, and the report includes charts showing the chronologic and geographic progress of the epidemic.

When it is remembered that the weekly charge of about 7s. made on every working member of the population not only provides the services of a doctor and a hospital but also entitles participation in all aspects of the Insurance Scheme outlined in this report it is small wonder that the burden on the Exchequer is vast.

John Lister, M.D.

London

## BOSTON MEDICAL LIBRARY

### MEDICAL STAMPS

Among the semipostal stamps issued in honor of physicians few equal the series of the Republic of Austria, produced in 1937. The portraits are fine examples of the engraver's art, and the subjects so skillfully depicted are among the great physicians of all time: Gerhard Freiherr von Swieten (1700–1772), Leopold Auenbrugger von Auenbrugg (1722–1809), Karl Freiherr von Rokitansky (1804–1878), Joseph Skoda (1805–1881), Ferdinand Ritter von Hebra (1816–1880), Ferdinand Ritter von Arlt (1812–1887), Joseph Hyrtl (1810–1894), Theodor Billroth (1829–1894) and Theodor Meynert (1833–1892). Auenbrugger lived longest (eighty-seven years); Meynert's life was the shortest (fifty-nine years). The average age was seventy-three, indicating that physicians even in the nineteenth century had a favorable expectancy of life.

## MASSACHUSETTS DEPARTMENT OF PUBLIC HEALTH

### COMMUNICABLE DISEASES IN MASSACHUSETTS FOR SEPTEMBER, 1952

Résumé

| Disease | September 1952 | September 1951 | Seven-Year Median |
|---|---|---|---|
| Chancroid | 1 | 1 | 2 |
| Chicken pox | 83 | 87 | 106 |
| Diphtheria | 0 | 2 | 10 |
| Dog bite | 1105 | 1050 | 980 |
| Dysentery, bacillary | 24 | 0 | 9 |
| German measles | 39 | 64 | 56 |
| Gonorrhea | 217 | 184 | 303 |
| Granuloma inguinale | 0 | 1 | 0 |
| Lymphogranuloma venereum | 0 | 1 | 1 |
| Malaria | 23 | 36 | 7 |
| Measles | 62 | 174 | 145 |
| Meningitis, meningococcal | 7 | 3 | 3 |
| Meningitis, Pfeiffer bacillus | 2 | 2 | 2 |
| Meningitis, pneumococcal | 0 | 2 | 1 |
| Meningitis, staphylococcal | 0 | 0 | 0 |
| Meningitis, streptococcal | 0 | 0 | 0 |
| Meningitis, undetermined | 8 | 3 | 2 |
| Mumps | 156 | 294 | 173 |
| Poliomyelitis | 161 | 69 | 147 |
| Salmonellosis | 14 | 11 | 10 |
| Scarlet fever | 62 | 53 | 105 |
| Syphilis | 126 | 156 | 156 |
| Tuberculosis, pulmonary | 205 | 159 | 200 |
| Tuberculosis, other forms | 7 | 8 | 14 |
| Typhoid fever | 2 | 2 | 1 |
| Undulant fever | 2 | 0 | 1 |
| Whooping cough | 109 | 191 | 463 |

Comment

Diseases below the seven-year median included chicken pox, diphtheria, German measles, measles, mumps and whooping cough.

For the thir consecutive month no cases of diphtheria were reported.

The 83 cases of chicken pox represented the lowest figure for any month since August, 1940.

With but one exception (September, 1949), the 62 cases of measles made this the lowest report for any month since September, 1937.

The 39 cases of German measles represented the lowest figure for September since 1944.

Diseases above the seven-year median were meningococcal meningitis and poliomyelitis.

The 161 cases of poliomyelitis, although above the seven-year median, represented a figure considerably lower than t he 602 cases reported in September, 1949.

### Geographical Distribution of Certain Diseases

The following diseases were reported from the communities named:

Anthrax was reported from: Lynn, 1.

Dysentery, amebic, was reported from: Foxboro, 1.

Dysentery, bacillary, was reported from: Boston, 3; Framingham, 1; Grafton, 4; Lowell, 4; New Bedford, 1; Waltham, 11; total, 24.

Hepatitis, infectious, was reported from: Boston, 1; Bourne, 1; Cambridge, 1; Camp Edwards, 1; Fort Devens, 2; Lancaster, 1; Newton, 1; Oxford, 1; Quincy, 1; Worcester, 24; Wrentham, 20; total, 54.

Lymphocytic choriomeningitis was reported from: Quincy, 1.

Malaria was reported from: Belmont, 1; Camp Edwards, 9; Fort Devens, 10; Somerville, 2; Weymouth, 1; total, 23.

Meningitis, meningococcal, was reported from Natick, 2; Springfield, 1; Westfield, 1; Winthrop, 1; Worcester, 2; total, 7.

Meningitis, Pfeiffer bacillus, was reported from: Northampton, 1; Sunderland, 1; total, 2.

Meningitis, mumps, was reported from: Lynnfield. 1.

Meningitis, undetermined, was reported from: Boston, 2; Clinton, 1; Dennis, 1; Fall River, 1; Lowell, 1; Springfield, 1; Worcester, 1; total, 8.

Poliomyelitis was reported from: Acton, 1; Agawam, 1; Amesbury, 1; Arlington, 1; Ashland, 1; Belmont, 2; Beverly, 1; Boston, 10; Braintree, 2; Brockton, 2; Cambridge, 2; Chatham, 1; Chelsea, 1; Chicopee, 1; Clinton, 2; Cohasset, 3; Danvers, 2; Dudley, 1; East Longmeadow, 1; Easton, 1; Falmouth, 1; Foxboro, 1; Framingham, 4; Franklin, 1; Greenfield, 1; Hardwick, 1; Hull, 1; Kingston, 1; Lakeville, 1; Lawrence, 5; Leominster, 1; Lexington, 1; Lowell, 7; Lynn, 7; Lynnfield, 2; Ludlow, 1; Malden, 1; Manchester, 1; Marblehead, 2; Marlboro, 1; Marshfield, 2; Medford, 4; Melrose, 1; Natick, 4; Needham, 2; New Bedford, 1; Newton, 4; Northampton, 2; North Andover, 1; Palmer, 1; Peabody, 3; Pittsfield, 2; Plymouth, 1; Quincy, 1; Revere, 1; Russell, 1; Salem, 6; Sandwich, 2; Sheffield, 1; Somerville, 5; Southwick, 1; Springfield, 8; Sutton, 1; Swampscott, 2; Tyngsboro, 1; Waltham, 1; Wellesley, 1; Westfield, 4; Westport, 1; West Springfield, 4; Westwood, 1; Weymouth, 2; Whitman, 1; Williamstown, 2; Winchester, 2; Woburn, 1; Worcester, 5; total, 161.

Salmonellosis was reported from: Beverly, 1; Boston, 4; Haverhill, 1; Lawrence, 1; Medford, 1; Melrose, 2; Newton, 2; Shrewsbury, 1; Worcester, 1; total, 14.

Septic sore throat was reported from: Boston, 5; Lowell, 1; total, 6.

Tetanus was reported from: Boston, 1.

Trichinosis was reported from: Boston, 2; Brockton, 2; New Bedford, 1; total, 5.

Tularemia was reported from Chilmark, 1 (delayed report).

Typhoid fever was reported from: Belmont, 1; New Bedford, 1; total, 2.

Undulant fever was reported from: Chicopee, 1; New Braintree, 1; total, 2.

## CORRESPONDENCE

### DOCTOR-DRAFT LAW

*To the Editor*: The editorial "Call To Active Duty" in the October 2 issue of the *Journal* is timely and well written. As far as I know this is the first medical journal to point up the confusion and lack of planning resulting from the "doctor-draft law."

As you know, not only are younger physicians in residencies being called up but also general practitioners of medicine in rural areas are being classified 1A. Time and money are involved in both situations. But what of the physician who, to provide some measure of security for his family, has geared his estate planning to two or three times the amount he could be paid while on active duty? What irreparable losses like lapsed life insurance, office location, practice and hospital-staff positions can be compensated for by vague talk about deferment on account of hardship and being essential? What yardstick may be employed? What definite set of rules and regulations may be applied objectively to point out who is essential and who is not? Has anyone attempted to define hardship?

There is no assurance that once a physician has entered the military service any skills he may have will be used. There is no indication that he will come out of the service any richer in experience and medical skill, but, quite to the contrary, there is indication that he will finally emerge older, poorer and, particularly if he is a general practitioner, less skilled than before

At present there seems to be no one who has the medium for wide dissemination of information who has been cognizant of the problem of the general practitioner in relation to military service. There is no expression that I know of from the American Medical Association or the American Academy of General Practice. At present there is little hope that any will be forthcoming because first confusion must be eliminated and clarity established.

J. Reginald Myers, M.D.

Everett, Pennsylvania

## NOTICES

### ANNOUNCEMENTS

Dr. Peter S. Zarecki, Jr., announces the removal of his office from 167 Maple Street to 95 State Street, Room 608, Springfield, for the practice of surgery.

Dr. Samuel H. Boyer announces the removal of his office from 483 Beacon Street to 520 Beacon Street, Boston. Practice limited to internal medicine and industrial hygiene.

### HARVARD MEDICAL SOCIETY

A meeting of the Harvard Medical Society will be held in the amphitheater of Building D, Harvard Medical School, on Wednesday, November 12, at 8 p.m. A program on the subject "New Knowledge of the Interactions of Proteins and of their Fine Structure" will be presented by the University Laboratory of Physical Chemistry Related to Medicine and Public Health, with Edwin J. Cohn presiding.

Program

Specific Interactions of Plasma Proteins with Blood Cells and Polysaccharides. Henry C. Isliker.

Specific Interactions of Plasma Proteins, Blood Cells and Viruses with Metals. Douglas M. Surgenor and S. S. Chapman.

Quantitative Aspects of the Interactions of Proteins with Metals. Frank R. N. Gurd.

Evidence Regarding the Fine Structure of Certain Plasma Proteins, Hormones and Viruses. Edwin J. Cohn.

### MASSACHUSETTS TRUDEAU SOCIETY

The fall meeting of the Massachusetts Trudeau Society will be held at the Boston Sanatorium, 249 River Street, Mattapan, on Thursday, November 13. There will be two sessions, one at 4 and the other at 8 p.m.

A new form of combined meeting (Pembine-conference type), consisting of a combined presentation of 10 consecutive cases in which collapse or surgical therapy was employed, will be presented by the staffs of the Boston Sanatorium and the Middlesex County Sanatorium. This will be followed by an informal discussion from the floor.

Physicians and medical students are cordially invited.

### ESSEX NORTH DISTRICT MEDICAL SOCIETY

The winter meeting of the Essex North District Medical Society will be held at the Pentucket Club, 111 Main Street, Haverhill, on Wednesday afternoon, January 14.

The annual meeting will be held at the Andover Country Club, Shawsheen, Andover, on Wednesday evening, May 13.

### AMERICAN COLLEGE OF CHEST PHYSICIANS

The nineteenth annual meeting of the American College of Chest Physicians will be held at the Hotel New Yorker, New York City, May 28–31. Physicians who wish to present papers at the meeting should submit titles and abstracts to Dr. Arthur M. Olsen, chairman, Committee on Scientific Program, American College of Chest Physicians, Mayo Clinic, Rochester, Minnesota.

## NEW YORK STATE SOCIETY OF ANESTHESIOLOGISTS

The sixth annual postgraduate assembly in anesthesiology of the New York State Society of Anesthesiologists will be held at the Hotel New Yorker, New York City, December 10–13.

As in previous years, the meeting will consist of scientific sessions, round-table discussions, technical and scientific exhibits and luncheons and dinners. The scientific sessions will be in panel form. The following subjects will be discussed:

Obstetric Anesthesia. Virginia Apgar, M.D.
Instruments of Medical Measurement. Albert Faulconer, M.D.
Temperature Regulation. Eugene F. Dubois, M.D.
Shock Syndrome — Mechanisms. Ephraim Shorr, M.D.
Respiratory Acidosis. Herbert C. Maier, M.D.
Consideration in the Use of Intravenous Fluids. Henry T. Randall, M. D.
Physiological Changes Accompanying Cardiovascular Surgery. George H. Humphreys, II, M.D.
Artificial Respiration. James L. Whittenberger, M.D.
Jurisprudence in Anesthesiology. Harry A. Gair, Esq., and Emile Z. Berman, Esq.

Registration forms for the Assembly may be obtained from the headquarters of the New York State Society of Anesthesiologists, 137 West 11th Street, New York 11, New York.

## AMERICAN BOARD OF OBSTETRICS AND GYNECOLOGY

The next scheduled examinations (Part II), oral and pathological, for all candidates will be held at the Edgewater Beach Hotel, Chicago, Illinois, by the entire Board from May 17, 1953, through May 24, 1953. Formal notice of the exact time of each candidate's examination will be sent him several weeks in advance of the examination dates. Requests for re-examination in Part II must be made prior to February 1, 1953, with the submission of data regarding additional training or experience and medical-school or hospital-staff appointments acquired in the interim.

Candidates currently applying for admission to the examinations for certification are required to submit a list of all patients for whom they have been solely responsible admitted to the hospitals where they practice, for the year preceding their application or the year prior to their request for reopening of their application, with the diagnosis, pathological diagnosis, nature of treatment and end result.

Dr. Lawrence M. Randall, who is assistant secretary of the American Board of Obstetrics and Gynecology, is in charge of all matters pertaining to residency training. All requests for information to be supplied by the American Board of Obstetrics and Gynecology regarding residency training should be addressed to Lawrence M. Randall, M.D., assistant secretary, American Board of Obstetrics and Gynecology, Mayo Clinic, Rochester, Minnesota.

Application forms for appraisal of incomplete training and for certification and requests for current bulletins should be made to Robert L. Faulkner, M.D., secretary, American Board of Obstetrics and Gynecology, 2105 Adelbert Road, Cleveland 6, Ohio.

## AMERICAN ACADEMY OF OBSTETRICS AND GYNECOLOGY

The first annual clinical session of the American Academy of Obstetrics and Gynecology will be held at the Palmer House, Chicago, December 15–17.

The meeting will feature six general sessions and 48 discussion groups of 40 fellows each. There also will be at least 15 new scientific exhibits and about 60 technical displays.

The annual banquet Tuesday evening, December 16, will feature an address by the retiring president, Dr. Carl P. Huber, of Indianapolis.

Election of officers will take place at the annual business meeting Tuesday morning.

## COURSES IN LABORATORY DIAGNOSIS OF TUBERCULOSIS

In co-operation with the Division of Chronic Disease and Tuberculosis, Public Health Service, the Bacteriology Laboratories of the Communicable Disease Center, Chamblee, Georgia, will offer two courses in the laboratory diagnosis of tuberculosis on the following dates: March 16–27 and November 16–27, 1953.

The courses are open to all grades of employed laboratory personnel who are approved by their state health officers. Practical laboratory training in all phases of tuberculosis bacteriology, including preparation of culture mediums, microscopy, cultural procedures, diagnostic use of animals and testing of drug sensitivity, will be offered in the course. No tuition of laboratory fees are charged. Reservations for the courses should be made well in advance.

Two similar courses will be given for laboratory directors, senior laboratory staff members, physicians and others of comparable professional standing on the following dates: March 30–April 3 and November 9–13, 1953.

Additional information and applications may be obtained from Laboratory Training Services, Communicable Disease Center, Public Health Service, P. O. Box 185, Chamblee, Georgia.

## SOCIETY MEETINGS AND CONFERENCES

October 6–December 8 and March 2–May 4. Massachusetts Department of Mental Health. Postgraduate Seminar in Neurology and Psychiatry. Page 540, issue of October 2.

October 7–December 9. Massachusetts Department of Mental Health. Course in Child Psychiatry (Pediatric Neuropsychiatry). Page 540, issue of October 2.

November 7–29. Springfield Hospital Educational Program. Page 623, issue of October 16.

November 7. Fifth Annual Harvard Lecture. Page 698, issue of October 30.

November 9 and 10. American Society for the Study of Arteriosclerosis. Page 78, issue of July 10.

November 10–13. International Medical Assembly. Page 584, issue of October 9.

November 10–21. Courses in Laboratory Diagnosis of Tuberculosis. Page 354, issue of February 28.

November 11. Springfield Academy of Medicine. Page 623, issue of October 16.

November 11–14. American Society of Anesthesiologists, Inc. Third Annual Refresher Course Program. The Bellevue-Stratford, Philadelphia.

November 12. New England Society of Psychiatry. Page 662, issue of October 23.

November 12. Lectures on Cancer Research. Page 697, issue of October 30.

November 12. Harvard Medical Society. Page 743.

November 12–December 17. Lahey Clinic Lectures. Page 698, issue of October 30.

November 13. Alpha Omega Alpha Lecture. Page 698, issue of October 30.

November 13. Massachusetts Trudeau Society. Page 743.

November 14 and 15. Diabetes Fair. Page 623, issue of October 16.

November 17. New England Cardiovascular Society. Page 698, issue of October 30.

November 17–19. Association of Military Surgeons of the United States. Page 583, issue of October 9.

November 17–March 23. Postgraduate Course in General Medicine. Page 697, issue of October 30.

November 18, February 6 and April 3. New England Society of Anesthesiologists. Page 418, issue of September 11.

November 19. New England Center Hospital House Officers' Association. Page 661, issue of October 23.

November 19. E. Stanley Emery Memorial Lecture. Page 662, issue of October 23.

November 19. New England Conferences on Allergy and Related Subjects. Page 697, issue of October 30.

November 19–April 8. Postgraduate Medical Institute. Page 452, issue of September 18.

November 21. New York Tuberculosis and Health Association. Page 583, issue of October 9.

November 25. Norfolk District Medical Society. Page 583, issue of October 9.

December 2. Lecture on Cancer Research. Page 697, issue of October 30.

December 10–13. New York State Society of Anesthesiologists. Notice above.

December 12 and 13. Association for Research in Nervous and Mental Disease. Page 584, issue of October 9.

December 15–17. American Academy of Obstetrics and Gynecology Notice above.

January 14, 1953. Essex North District Medical Society. Notice above.

March 16–27 and November 16–27. Courses in Laboratory Diagnosis of Tuberculosis. Notice above.

March 30–April 3 and November 9–13. Courses for Laboratory Directors, Senior Laboratory Staff Members and Physicians. Notice above.

May 13. Essex North District Medical Society. Page 743.

May 19–21. Massachusetts Medical Society. Hotel Statler, Boston.

May 28. American College of Chest Physicians. Page 743.

August 24–28. Eighth International Congress on Rheumatic Diseases. Page 584, issue of October 9.

(*Notices concluded on page xxi*)